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## Cancer The'RBPeutics – RNA-Binding Proteins as Therapeutic Targets for Cancer

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### Abstract

RNA-binding proteins (RBPs) play a critical role in the regulation of various RNA processes, including splicing, cleavage and polyadenylation, transport, translation and degradation of coding RNAs, non-coding RNAs and microRNAs. Recent studies indicate that RBPs not only play an instrumental role in normal cellular processes but have also emerged as major players in the development and spread of cancer. Herein, we review the current knowledge about RNA binding proteins and their role in tumorigenesis as well as the potential to target RBPs for cancer therapeutics.

### Keywords

RNA-Binding Proteins; RNA-Binding Domains; cancer therapeutics; small molecules; siRNA; peptide; aptamer

### 1. INTRODUCTION

A majority of eukaryotic genes are regulated at transcriptional and post-transcriptional levels, giving each one a unique expression profile under specific conditions (K. Chen & Rajewsky, 2007; Orphanides & Reinberg, 2002). Once an mRNA is transcribed, it is subjected to various processing, mainly controlled by RNA-binding proteins (RBPs) (Keene, 2007). RBPs coordinately bind to each mRNA and form ribonucleoprotein (RNP) complexes. The composition of the RNP complexes is dynamic based on the specific RNA processing. Notably, although RBPs bind to various classes of RNAs such as ribosomal RNAs, mRNAs, snRNA, snoRNA, tRNAs, and non-coding RNAs, about half of the RBPs manifest their function by binding to mRNAs and exert their distinct roles in regulating mRNA fate (Jin Zhang & Chen, 2008). Given the important role of RBPs in various cellular processes, such as transcription, splicing, mRNA stability, mRNA transport and translation,

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#### CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

it comes as no surprise that alterations in RBP expression or RBP mutations can lead to various diseases, including cancer (Kechavarzi & Janga, 2014; Neelamraju, Gonzalez-Perez, Bhat-Nakshatri, Nakshatri, & Janga, 2018; Pereira, Billaud, & Almeida, 2017). Indeed, recent studies have found that altered expression, localization or post-translational modification of RBPs can contribute to tumorigenesis by not only increasing expression of oncogenes but also decreasing the expression of tumor suppressor genes. Thus, increasing attention has been paid to the roles of RBPs in cancer as well as the potential of targeting RBPs for cancer therapeutics. In this review, we will discuss the functional domains of various RBPs and their roles in malignant transformation. We will also discuss recent advances and new insights into targeting RBPs for cancer therapeutics.

## 2. RNA-BINDING DOMAINS

RBPs were initially identified due to their capability to bind various types of RNAs through an RNA-binding domain (RBD) that forms steady secondary and tertiary structures. The classical RBDs include the K-homology domain (KH), RNA recognition motif (RRM), Zinc finger domain (ZNF), Pumilio homology domain (PUM), double stranded RNA binding domain (dsRBD), and others (Figure 1) (Lunde, Moore, & Varani, 2007). Due to the recently developed high-throughput approaches, the number of RBPs has been largely increased to 1542 (Baltz et al., 2012; Castello et al., 2012; Gerstberger, Hafner, & Tuschl, 2014; Z. L. Wang et al., 2018), comprising about ~7.5% of the protein coding genes. Interestingly, among them, only a quarter of RBPs contain classical RNA-binding domains (RBDs) and the rest of them contain non-canonical RBDs that have previously uncharacterized motifs (Baltz et al., 2012). These non-canonical RBPs are unique in that they have intrinsically disordered regions that adapt their structure upon contacting to RNAs and subsequently mediate cell cycle regulation, metabolism, and signal transduction. For this section, we focus on some of the classical RNA-binding domains present in canonical RBPs. For the non-canonical RBPs, readers are referred to these recent reviews (Hentze, Castello, Schwarzl, & Preiss, 2018; Moore, Jarvelin, Davis, Bond, & Castello, 2018).

### 2.1. RNA Recognition Motif (RRM)

RNA-recognition motif (RRM), also called as ribonucleoprotein (RNP) domain, is one of the most abundant and classical RNA-binding domain present in a number of RBPs (Maris, Dominguez, & Allain, 2005). Their abundance and early discovery also make them the most studied RBD with more than 30 solved crystal structures of RRM bound to their target RNA sequences. (Sickmier et al., 2006; X. Wang & Tanaka Hall, 2001). Each RRM is made up of about 90 amino acids and consists of two conserved sub-motifs referred to as RNP1 and RNP2. RNP1 consists of 8 amino acids with the consensus sequences, (R/K)-G-(F/Y)-(G/A)-(F/Y)-V-X-(F/Y), whereas RNP2 contains 6 amino acids with the consensus sequences, (L/I)-(F/Y)-(V/I)-X-(N/G)-L. Structurally, the RRM domain is composed of four anti-parallel  $\beta$  sheets stacked against two  $\alpha$  helices, giving it the  $\beta_1\alpha_1\beta_2\beta_3\alpha_2\beta_4$  topology with RNP1 and RNP2 motifs making the central  $\beta_3$  and  $\beta_1$  sheets, respectively. Most of the RRM domains contain three conserved aromatic amino acids in the central  $\beta$  strands, which allow for the recognition of two nucleotides. Some RRM domains lack one or more of the conserved aromatic residues forming the derivative RRM domains such as the quasi-RRM, the pseudo-

RRM or U2AF homology motifs. Additional nucleotides can be recognized by the RRM using other aromatic and planar side-chains present on other  $\beta$  strands. In general, each RRM domain can recognize anywhere between 4 to 8 nucleotides by using  $\beta$ -sheet surface extensions or by using exposed loops connecting  $\beta$ -sheet to a  $\beta$ -sheet or  $\alpha$ -helix. To achieve sequence specificity and affinity for an mRNA, RBPs generally contain more than one RRM and bind RNA cooperatively. This has been demonstrated with the structures of several tandem RRMs bound to RNA, such as HuD and nucleolin (Allain, Bouvet, Dieckmann, & Feigon, 2000; Wang & Tanaka Hall, 2001). In other cases, some RRMs do not coordinate with each other and appear to bind RNA independently. For example, the RRM1 and RRM2 in PTB are clearly independent from each other and are separated by long flexible linkers (Oberstrass et al., 2005). The different binding affinity among RRMs may be critical for target selection.

## 2.2. hnRNP-K-Homology domain (KH domain)

The heterogeneous nuclear ribonucleoprotein (hnRNP) K-homology (KH) domain is approximately 70 amino acids long and was initially identified in the human hnRNP-K protein more than two decades ago (Siomi, Matunis, Michael, & Dreyfuss, 1993). There are two types of KH domains: the eukaryotic type I and prokaryotic type II, both of which comprise of three  $\alpha$ -helices and a three-stranded anti-parallel  $\beta$ -sheets (Grishin, 2001; Valverde, Edwards, & Regan, 2008). While both type I and type II share a minimal  $\beta\alpha\alpha\beta$  core, they fold differently due to the location of additional  $\alpha$  and  $\beta$  elements. In the type I KH domain, the  $\alpha$  and  $\beta$  elements are located at the C-terminus, whereas in the type II KH domain, these elements are located at the N-terminus. Additionally, KH domain contains a conserved "GXXG" loop motif and a variable loop. KH domain interacts with nucleotides through hydrogen bonds, electrostatic interactions, and shape complementarity. Generally, each KH domain can recognize four nucleotides through a binding cleft formed by the  $\alpha 1$  and  $\alpha 2$  helices linked by the "GXXG" loop on one side and the  $\beta$ -sheet and the variable loop on the other side. For example, Nova2 (Neuro-oncological ventral antigen 2) is a tissue-specific alternative splicing factor and contains three type I KH domains. The crystal structure of the KH3 domain in complex with RNA shows that Nova2 interacts with the single stranded UCAC motif (Lewis et al., 2000). Additionally, the KH3 domain in PCBP2 recognizes the CCCT motif whereas the KH3 domain in hnRNP K binds to TCCC motif (Du et al., 2007). Sometimes, the KH domains in the same RBP can recognize different motifs. For instance, the KH1 domain in NusA RBP recognizes AGAA motif whereas its KH2 domain recognizes CAAU motif (Beuth, Pennell, Arnvig, Martin, & Taylor, 2005). These structural analyses indicate that KH domains are versatile in recognizing a large panel of sequences; however, its affinity and specificity of interaction is low. Thus, at least two strategies are selected by KH domain containing RBPs to overcome this. The first strategy is to extend the surface of interaction with nucleic acids. For example, the binding interface in SF1/mBBP is composed of a KH domain along with a C-terminal helix, known as the QUA2 domain (Z Liu et al., 2001). As a result, SF1 specifically binds to the six nucleotide sequence 5'-UACUAAC-3' (Berglund, Chua, Abovich, Reed, & Rosbash, 1997). The second strategy is the repetition of multiple KH domains within a single RNA binding protein, which is a common feature in most KH domain containing RBPs. In general, multiple copies of KH domains can act in synergy and interact efficiently with their target.

For example, the two KH domains of NusA together show stronger binding than each separated (Beuth et al., 2005). However, there are also exceptions. FUSE-binding protein (FBP) contains four KH domains and are separated by a longer linker indicating that each domain recognizes RNA independently (Braddock, Louis, Baber, Levens, & Clore, 2002). Thus, each KH domain binds separately to its target.

### 2.3. Zinc-Finger domain

Discovered more than 30 years ago as classical DNA-binding proteins, zinc fingers proteins were subsequently found to bind RNAs as demonstrated by their crystal structure (Hudson, Martinez-Yamout, Dyson, & Wright, 2004; D. Lu, Searles, & Klug, 2003). Each zinc finger consists of about 25–30 amino acids and forms a  $\beta\beta\alpha$  topology that is held together by the central  $Zn^{2+}$  ion. They are generally classified based on the amino acid residues coordinating the  $Zn^{2+}$  atom, e.g., CCHH, CHCC, CCCH, CCHC, or CCCC, with the CCHH being the most frequent type. Transcription factor TFIIIA was the first zinc finger containing protein that was initially discovered through its association with 5S rRNA (Searles, Lu, & Klug, 2000). TFIIIA contains nine zinc fingers: zinc fingers 1–3, 5 and 7–9 bind DNA, zinc fingers 4–6 contact RNA, whereas zinc finger 5 contacts both DNA and RNA. The CCHH-type zinc fingers interact directly with the major groove of DNA by forming hydrogen bonding with the Watson-Crick base pairings through the side chains of variable residues present in their  $\alpha$ -helix. Unlike other domains that use  $\beta$ -sheet to recognize RNA, the zinc finger uses the exposed loops and  $\alpha$ -helices for the recognition. Other versatile modes of interaction of zinc fingers with RNA have also been reported. For example, TIS11d, a member of the tristetraprolin (TTP) protein family contains two CCCH zinc fingers and mediates mRNA degradation via binding to an AU-rich element (ARE) in mRNA 3'-UTRs (Blackshear, 2002). Structural studies show that each zinc finger of TIS11d can specifically recognize an 'UAU' motif primarily through hydrogen bonds between the protein backbone and the RNA bases. MBNL1, another zinc finger protein, contains four CCCH zinc fingers and binds RNA (Pascual, Vicente, Monferrer, & Artero, 2006). The preferential binding of zinc fingers 3 and 4 of MBNL1 to 'GC' and 'GCU' RNA motifs, respectively, is mediated by stacking interactions and several hydrogen bonds involving main chains. These structure data indicate that zinc fingers can specifically bind single-stranded RNA, primarily using hydrogen bonds and aromatic-base stacking interactions. Moreover, these domains are more plastic and flexible which allows them to acquire different conformations to accommodate various sequences.

### 2.4. Double-stranded RNA binding domain

The double stranded RNA binding domain (dsRBD) is found in both prokaryotes and eukaryotes and controls diverse RNA related functions such as RNA interference, localization, editing and translocation. The dsRBD typically consists of 70–90 amino acids and displays a distinctive  $\alpha\beta\beta\beta\alpha$  protein folding pattern (Bycroft, Grunert, Murzin, Proctor, & St Johnston, 1995; Nanduri, Carpick, Yang, Williams, & Qin, 1998; Ryter & Schultz, 1998). Notably, unlike other RBDs, most dsRBDs recognize the shape of the dsRNA rather than the RNA sequence. As observed from the crystal structure of RBP Xlrbpa complexed with synthetic dsRNA (Ryter & Schultz, 1998), the interaction mostly involves RNA's phosphodiester backbone and its ribose 2'-OH groups, which explains why dsRBDs bind to

dsRNA mainly dependent upon the structure rather than the sequence (Ryter & Schultz, 1998). In most cases, dsRBDs interact with a regular RNA A-form helix structure, composed of a major groove and two consecutive minor grooves. Additionally, dsRBDs also bind to single-stranded RNAs with bulges or mismatches (B. Tian et al., 2000). Like other RBDs, dsRBDs are often present in multiple copies in an RNA-binding protein, conferring some specificity for certain RNA secondary structures. Interestingly, despite the conservation in both sequence and structure, some dsRBDs show strong binding with various dsRNAs whereas others show weak affinity for dsRNAs. Additionally, although most dsRBDs recognize RNA shape, the solution structure of dsRBD2 of ADAR2 showed dsRNA recognition not only by shape of the RNA but also by the sequence (Stefl et al., 2010). ADAR2 is an adenosine deaminase that converts adenosine-to-inosine (A-to-I) by hydrolytic deamination in numerous mRNA and pre-mRNA transcripts.

## 2.5. Piwi/Argonaute/Zwille (PAZ) and Piwi domains

The PAZ domain is approximately 140 amino acids in length and is named after three proteins-Piwi, Argonaute, and Zwille. PAZ domains are commonly found in proteins involved in miRNA biogenesis, such as Dicer and Ago. In 2003, three groups determined the PAZ domain structures concurrently (Lingel, Simon, Izaurralde, & Sattler, 2003; J. J. Song et al., 2003; K. S. Yan et al., 2003). The PAZ domain structures contain two subdomains with a prominent cleft between. The larger subdomain has a fold that is reminiscent of oligonucleotide/oligosaccharide binding (OB) fold, although with slightly different topology, and the second subdomain, called by some “the appendage,” is composed of a  $\beta$ -hairpin followed by an  $\alpha$ -helix. Since a majority of the OB-fold proteins bind single-stranded oligonucleotides or oligosaccharides, the initial PAZ domain structures suggested its role in nucleic acid binding. Later studies confirmed the mode of PAZ-siRNA recognition by the structures of PAZ domain in complex with 3' overhanging ends of siRNAs (Lingel, Simon, Izaurralde, & Sattler, 2004; J. B. Ma, Ye, & Patel, 2004).

The Piwi domain is only present in Argonaute proteins and its crystal structure revealed that it clearly belongs to the RNase H family of enzymes (J. J. Song, Smith, Hannon, & Joshua-Tor, 2004), comprising a five-stranded mixed  $\beta$  sheet surrounded by  $\alpha$  helices on both sides. RNase H enzymes are known to cleave the RNA strand of an RNA–DNA hybrid (W. Yang & Steitz, 1995). In addition to its core RNase H fold, Piwi domain contains two highly conserved aspartates always present on adjacent  $\beta$ -strands. Mutation of each of these aspartates eliminates the slicer activity of Argonaute2 (J. Liu et al., 2004; Rivas et al., 2005). Piwi domains have high affinities for ssDNA, medium affinities for RNA/DNA and dsDNA, and the lowest for dsRNA and ssRNA (J. B. Ma et al., 2005; Yuan et al., 2005).

## 2.6. S1 domain

The S1 domain was originally identified in ribosomal protein S1, but has since been found in a large number of RNA-associated proteins (Subramanian, 1983). The *E. coli* S1 protein consists of six S1 domains folded into five-stranded anti-parallel  $\beta$ -barrel, which are involved in RNA binding (Bycroft, Hubbard, Proctor, Freund, & Murzin, 1997). The fold in S1 domain is similar to the oligonucleotide/oligosaccharide binding (OB)-fold superfamily (Flynn & Zou, 2010; Theobald, Mitton-Fry, & Wuttke, 2003). The nucleic acid binding of

S1 domain requires a two-stranded  $\beta$ -sheet core along with the surrounding loops and secondary structure elements (Schubert et al., 2004).

## 2.7. DEAD-box domain

DEAD box proteins form the largest helicase family (Fairman-Williams, Guenther, & Jankowsky, 2010) and are characterized by the presence of an Asp- Glu- Ala- Asp (DEAD) motif. DEAD box helicases play a central role in cellular RNA metabolism and generally function as part of larger multicomponent assemblies, such as the spliceosome or the eukaryotic translation initiation machinery (Linder & Jankowsky, 2011). Several crystal structures of helicases from the various superfamilies have been obtained and indicate that DEAD box proteins contain two covalently linked globular domains, each of which generally contains five  $\beta$ -strands surrounded by five  $\alpha$ -helices, resembling the folding of the RecA ATPase (Andersen et al., 2006). There are at least 12 characteristic sequence motifs located at conserved positions, with the DEAD box located at Motif II. Structural analysis revealed that all the DEAD box proteins utilize a highly conserved mode of RNA binding (Del Campo & Lambowitz, 2009; Sengoku, Nureki, Nakamura, Kobayashi, & Yokoyama, 2006), whereby the helicase core mediates the contacts exclusively to the sugar phosphate backbone of the RNA. In addition to its helicase core, the core DEAD box proteins contain variable auxiliary domains, which are located at C- and N-terminals. These domains are thought to be critical for the diverse functions of these enzymes, e.g., allowing interaction with other proteins or with RNA targets.

## 3. ABERRANT EXPRESSION OF RBPS IN CANCER

Altered RNA metabolism due to an RBP malfunction can lead to genome-wide changes in the transcriptome and proteome of the cells and subsequently, affect cell growth, proliferation, invasion and death. Thus, it is not a surprise that altered expression of RBPs is a common phenomenon during development and progression of cancers. Thus, a table is provided to briefly elucidate the alteration of these RBPs in cancer (See Table 1). In this section, we will focus on several RBP families and their emerging roles in cancer.

### 3.1. The RBM38 and RBM24 family proteins

The RNA-binding proteins RBM38 and RBM24 share a high degree of homology and thus constitute a family of single RRM-containing RNA-binding proteins (Y. Jiang et al., 2014; Shu, Yan, & Chen, 2006). RBM38 and RBM24 are known to regulate many aspects of mRNA metabolism, including splicing, mRNA stability and translation (Heinicke et al., 2013; Miyamoto, Hidaka, Jin, & Morisaki, 2009; Ohe et al., 2017; J Zhang et al., 2014; M. Zhang et al., 2018). Notably, RBM38 and RBM24 contain an identical RRM and prefer to bind to AU/U-rich elements in target mRNAs, suggesting that these two proteins have similar functions through modulating the same targets. For example, both RBM38 and RBM24 can be induced by tumor suppressor p53 and in turn repress p53 mRNA translation (J Zhang et al., 2011; M. Zhang et al., 2018). Other targets that can be regulated by RBM38 and RBM24 include p21 and p63 (Cho, Zhang, & Chen, 2010; Y. Jiang et al., 2014; Miyamoto et al., 2009; Shu et al., 2006; E. Xu et al., 2014; J Zhang, Jun Cho, & Chen, 2010). Despite these common features, the tissue expression profile of RBM24 differs from



that of RBM38. RBM24 is mainly expressed in muscle and heart whereas RBM38 is highly expressed in lymphatic tissues, such as spleen, thymus and bone marrow. In addition, *Rbm24*-KO mice are embryonic lethal whereas *Rbm38*-null mice are born alive but prone to hematopoietic defects and spontaneous tumors (van den Hoogenhof et al., 2017; J Yang et al., 2014; J Zhang et al., 2014; M. Zhang et al., 2018). These data indicate that both the proteins have non-redundant functions.

RBM38 has been implicated in cancer development and its expression is found to be altered in several different kinds of cancers. For example, RBM38 is suggested to be a tumor suppressor in hepatocellular carcinoma, non-small cell lung cancer and renal cell carcinoma (Ding et al., 2014; W. Huang et al., 2017; L. Yang, Zhang, Ling, & Heng, 2018). Similarly, other studies indicated a tumor suppressor function of RBM38 in breast cancers and demonstrated that RBM38 is down-regulated in breast cancers by promoter hypermethylation (Leveille et al., 2011; J. Q. Xue et al., 2014). Similarly, another study showed that high expression of RBM38 in ovarian cancer, breast cancer and glioma is associated with better patient survival (Feldstein, Ben-Hamo, Bashari, Efroni, & Ginsberg, 2012). However, we showed that RBM38 is over-expressed in canine lymphoma, which is associated with low expression of p53 (J Zhang et al., 2011). Additionally, high expression of RBM38 was found to be associated with poor prognosis in breast cancer and with malignant transformation of colorectal adenoma to carcinoma (Carvalho et al., 2009; Chin et al., 2006; Hermsen et al., 2002; Jenssen, Kuo, Stokke, & Hovig, 2002). These apparent opposing data about the role of RBM38 in tumorigenesis could be explained by the fact that RBM38 might regulate unique targets in different cancers. In line with this, RBM38 was found to regulate multiple tumor suppressors as well as oncogenes, including MDM2, GDF15, HuR, HIF1, ER, PR, ZO-1, and PTEN (Cho et al., 2015, 2010; Lou et al., 2017; L. Shi et al., 2015; E. Xu, Zhang, & Chen, 2013; T. Yin, Cho, & Chen, 2013; J Zhang et al., 2018). Thus, the role of RBM38 in tumorigenesis could be context dependent. Indeed, we showed that depending on the p53 status, RBM38 can either promote or suppress tumor formation since RBM38 represses both wild-type and mutant p53 expression via mRNA translation (J Zhang et al., 2014). By using multiple mouse models, we showed loss of RBM38 decreases the tumor penetrance of p53 heterozygous mice, presumably through enhancing wild-type p53 expression (J Zhang et al., 2014). On the contrary, in a mutant p53 background, RBM38 KO promotes tumor incidence and tumorigenesis (J Zhang et al., 2018). Taken together, RBM38 is an important RBP that plays a vital role in normal physiology and shows altered expression and function in various cancers.

The role of RBM24 in cancer is much less studied compared to RBM38. To date, the biological function of RBM24 is found to be involved in skeletal muscle differentiation by regulating p21, MyoD and myogenin expression (Y. Jiang et al., 2014; Jin, Hidaka, Shirai, & Morisaki, 2010; H. Li, Bourdelas, Carron, & Shi, 2010; Miyamoto et al., 2009). Additionally, RBM24 is found to be involved in sarcomeric assembly and cardiac contractility (Maragh et al., 2011; Poon et al., 2012). Consistent with these findings, we and others showed that loss of RBM24 leads to multiple cardiac malfunctions in mice (J Yang et al., 2014; M. Zhang et al., 2018), suggesting that RBM24 plays a critical role in the early stages of heart development. Despite its critical role in heart development, several lines of evidence suggest that RBM24 plays a role in tumorigenesis. For example, a recent study

indicated RBM24 expression was found to be frequently down-regulated across 15 cancer types compared to normal tissues (Z. L. Wang et al., 2018). Consistent with this, RBM24 was found to suppress cancer progression by up-regulating miR-25 in nasopharyngeal carcinoma (W. F. Hua et al., 2016). However, we showed previously that RBM24 represses tumor suppressors, including p53 and p63 (E. Xu et al., 2014; M. Zhang et al., 2018), suggesting that RBM24 may function as an oncogene. Thus, the role of RBM24 in cancer may be complicated by its regulation of multiple targets involved in tumor suppression or promotion.

### 3.2. The PCBP family proteins

The PCBP family of proteins consists of hnRNP K and PCBP-1, 2, 3, 4, and belong to the KH domain superfamily of nucleic acid-binding proteins. All PCBP family proteins contain three KH domains and are unique in their high affinity for tracts of poly-cytosine (Poly-C binding specificity). Notably, PCBP1 is an intron-less gene and thought to be produced by retro-transposition of a PCBP2 splicing transcript (Makeyev, Chkheidze, & Liebhaber, 1999). Thus, PCBP1 and PCBP2 share the highest level of amino acid sequence identity (~82%) among all the members. Additionally, PCBP3 and PCBP4 share 64% and 45% homology with PCBP2, respectively. PCBP family proteins have broad functions involving transcriptional regulation and mRNA metabolism (H. S. Choi et al., 2009; Makeyev & Liebhaber, 2002). Recently, PCBP1 and PCBP2 were also identified as cytosolic iron chaperones that deliver iron to ferritin (Leidgens et al., 2013; H. Shi, Bencze, Stemmler, & Philpott, 2008). Compared with other members, the biological function of PCBP3 is much less understood. PCBP3 was found to repress mu opioid receptor gene by binding to double stranded poly(C) element (H. S. Choi et al., 2007; S. S. Kim et al., 2005) and may be involved in spermiogenesis (Chapman et al., 2013). Recently, PCBP3 was suggested to be a favorable prognostic marker for pancreatic cancer prognosis (Ger et al., 2018). Thus, we will focus on the role of PCBP1, PCBP2, PCBP4 and hnRNP K in tumorigenesis. Interestingly, although PCBP proteins share high sequence similarity, they appear to have opposing roles in tumorigenesis. PCBP1 and PCBP4 are thought to function as tumor suppressors whereas PCBP2 and hnRNP K function as oncogenes (J. Guo & Jia, 2018).

PCBP1 is shown to be down-regulated in various types of cancers, such as lung cancer, cervical cancer, breast cancer, colon cancer, and liver cancer (Pillai et al., 2003; Thakur et al., 2003; H. Wang et al., 2010; T. Zhang et al., 2010). In line with this, high expression of PCBP1 is associated with good prognosis in patients diagnosed with lung cancer and acute myeloid leukemia (Y. Liu et al., 2015; M. Zhou & Tong, 2015). The tumor suppressive function of PCBP1 is probably due to its regulation of many targets involved in cancer development. For example, one study showed that PCBP1 inhibits tumorigenesis through translationally repressing PRL-3 phosphatase (H. Wang et al., 2010). PRL-3 is a multitasking phosphatase involved in multiple steps of cancer progression, especially in cancer metastasis (Saha et al., 2001; Zeng, Hong, & Tan, 1998). In addition, PCBP1 was found to increase p27 mRNA stability and translation (H. Shi et al., 2018) but suppressed expression of MAPK1 (Y Zhang et al., 2018). However, studies from the PCBP1-null mice did not provide direct evidence that PCBP1 is a tumor suppressor. PCBP1-null mice are embryonic lethal at the pre-implantation stage whereas PCBP1-het mice are viable but prone



to a postnatal weight gain defect (Ghanem et al., 2016). Later, it was found that conditional PCBP1 deficiency leads to microcytic anemia in mice and is linked to auto-inflammatory diseases (Ryu, Zhang, Protchenko, Shakoury-Elizeh, & Philpott, 2017; Z. Wang et al., 2018), both of which are known to be related to cancer.

Similar to PCBP1, several lines of evidence indicate that PCBP4 can function as a tumor suppressor. First, the PCBP4 gene is located on chromosome 3p21 and loss of chromosome 3p21 is one of the most prevalent genomic abnormalities in lung cancer (Dammann et al., 2000; Tai et al., 2006). Moreover, PCBP4 was also found to be down-regulated in several types of cancers, including lung cancer (Pio et al., 2004). Consistent with this, over-expression of PCBP4 inhibits proliferation of lung cancer cells (Castano, Vergara-Irigaray, Pajares, Montuenga, & Pio, 2008; J. Zhu & Chen, 2000). Furthermore, our group generated PCBP4-null mice and found that these mice are prone to lung cancer and lymphoma (W. Yan et al., 2016). The tumor suppressive function of PCBP4 is at least in part due to its regulation of several targets that are known to be critical for tumor suppression. For example, we showed that PCBP4 is required for the expression of tumor suppressor p53 by modulating p53 stability via ZFP871 (W. Yan et al., 2016). We also showed that PCBP4 is required for maintaining the stability of p21 mRNA (Scoumanne, Cho, Zhang, & Chen, 2011). Nevertheless, more studies are needed to further elucidate the role of PCBP4 in tumor suppression.

PCBP2 was found to be up-regulated in several types of cancers, such as gastric cancer, esophageal cancer, glioblastoma, and HCC (Hu, Liu, Zhang, & Huang, 2014; Luo & Zhuang, 2017; J Ye et al., 2016; X Zhang et al., 2016). Consistent with this, knockdown of PCBP2 inhibited glioma cell growth both in vitro and in nude mice (W. Han et al., 2013). Several targets of PCBP2 have been identified, which might explain the tumor promoting function of PCBP2. For example, PCBP2 was able to destabilize the mRNA of four-and-a-half LIM domain 3 (FHL3), which inhibits glioma cell growth (W. Han et al., 2013). Additionally, PCBP2 was found to enhance the binding of miR-151-5p and miR-16 to ARHGDI1A (rho GDP dissociation inhibitor alpha, a metastasis suppressor) and subsequently, shown to facilitate the migration and invasion of glioma cells (X. Lin et al., 2016). However, other studies indicate that PCBP2 may function as a tumor suppressor. For example, we found that PCBP2 is required for the expression of TAp73, a member of the p53 tumor suppressor family and mediates p73-dependent antioxidant defense (Ren, Zhang, Yan, Zhang, & Chen, 2016). Additionally, PCBP2 was found to form a complex with the Hippo pathway components and suppress growth in breast epithelial cells (F. Li, Bullough, Vashisht, Wohlschlegel, & Philpott, 2016). Moreover, PCBP2-null mice die between E12.5 and E15.5 with hemorrhage and edema (Ghanem et al., 2016), which also make it difficult to study the role of PCBP2 in tumorigenesis by using conventional knockout mouse models.

Similar to PCBP2, hnRNP K is also found to be up-regulated in cancers including bladder cancer, gastric cancer, melanoma, prostate cancer, nasopharyngeal cancer, and oral squamous cell carcinoma (L. C. Chen et al., 2008; X. Chen et al., 2017; Nagano et al., 2004; Wen et al., 2010; C. S. Wu et al., 2012; R. Yang et al., 2016). Consistent with these findings, hnRNP K was found to facilitate the expression of several oncogenes, such as c-Myc and Src (Adolph, Flach, Mueller, Ostareck, & Ostareck-Lederer, 2007; Evans et al., 2003).

Additionally, hnRNP K is required for colon cancer survival by modulating MRPL33 (L. Liu et al., 2018). Despite clinical data suggesting that hnRNP K functions as an oncogene, studies have also showed that hnRNP K impacts tumor suppressor pathways, including the p53 pathway (Enge et al., 2009; Moumen, Masterson, O'Connor, & Jackson, 2005) and mediates tumor suppression. Indeed, hnRNP K was found to be one of genes that are frequently deleted in patients with acute myeloid leukemia (AML) (Dayyani et al., 2008; Sweetser et al., 2005), consistent with its tumor suppressive roles. Moreover, hnRNP K haploinsufficient mice are tumor prone and have reduced survival and most importantly, these mice mimic the putative haploinsufficiency observed in AML patients with 9q21.32 deletions (Gallardo et al., 2015). Together, these data suggest that hnRNP K has both oncogenic and tumor suppressive functions and may exert these functions in a tissue-specific manner.

### 3.4. The tristetraprolin (TIS11/TTP) family

The Tristetraprolin gene (TIS11, TTP, ZFP36, NUP475, GOS24) was initially identified as a TPA (12-O-tetradecanoylphorbol-13-acetate) inducible sequence in cultured murine fibroblasts (Q. Ma & Herschman, 1991; Varnum, Lim, Sukhatme, & Herschman, 1989). Later, it was found that TIS11 belongs to a small family of RNA binding proteins containing tandem CCCH zinc fingers (Ciais, Cherradi, & Feige, 2013). The human TIS11 family consists of three members TIS11, TIS11b (Berg36, ERF-1, ZFP36L1, BRF-1), and TIS11d (ZFP36L2, ERF-2, BRF-2). A fourth family member, Zfp36l3, is only expressed in mouse placenta, but is not detected in human placenta or other human tissues (Blackshear et al., 2005; Frederick, Ramos, & Blackshear, 2008). TIS11 family members share two highly conserved CCCH tandem zinc fingers preceded by an YKTEL motif, which is necessary for their RNA binding activities (Hudson et al., 2004; Lai, Carballo, Thorn, Kennington, & Blackshear, 2000). TIS11 family members can bind directly to AU-rich elements within mRNAs, and then promote decay of those mRNAs and/or inhibit their translation (Baou, Jewell, & Murphy, 2009). The mRNA decay mediated by TIS11 is carried out by multiple mechanisms. For example, TIS11 and TIS11b recruit and associate with the decapping enzymes Dcp1 and Dcp2 (Lykke-Andersen & Wagner, 2005). Additionally, TIS11 associates indirectly with poly(A)-specific ribonuclease (PARN), resulting in de-adenylation and destabilization of target mRNAs (Lai, Kennington, & Blackshear, 2003).

Based on the studies from knockout mouse models, it seems that all TIS family proteins have a broad role in various biological processes. For example, TIS11 was first found to be involved in inflammatory disease. TIS11-null mice appeared normal at birth, but soon developed a systemic autoimmune inflammatory syndrome due to TNF- $\alpha$  overproduction, which can be rescued by injection of the mice with anti-TNF $\alpha$  antibodies shortly after birth (Taylor et al., 1996). TIS11b-null mice died mid-gestation and exhibited extraembryonic and intraembryonic vascular abnormalities and heart defects, which is due to elevated expression of vascular endothelial growth factor (VEGF)-A (Bell et al., 2006; Stumpo et al., 2004). TIS11d knock-out mice are viable for approximately 2 weeks after birth and exhibit significant defects in hematopoiesis, resulting in anemia and thrombocytopenia (Stumpo et al., 2009). These different phenotypes observed from germline ablation of Tis11 family

members suggests that they have unique role during development by modulating their own specific targets despite their highly conserved RNA binding domains.

Many targets have been identified that are regulated by the TIS11 family, most of which are involved in malignancy (Baou et al., 2009; Park, Lee, & Kang, 2018; Zanocco-Marani, 2010), suggesting a tumor suppressive function of the TIS11 family proteins. In support of this notion, TIS11 has been reported to be down-regulated in several human cancers and suppresses cancer (Milke et al., 2013; Wei et al., 2016). Taken together, these observations suggest that the TIS11 family proteins have a vital role in human cancers.

### 3.5. The Musashi RBPs

The Musashi (MSI) RBP was first identified in *Drosophila* due to its role in regulating asymmetrical division of *Drosophila* sensory organ precursor (SOP) cells (Nakamura, Okano, Blendy, & Montell, 1994). The *Musashi* gene is evolutionary conserved: mammals contain two Musashi homologs: Musashi-1 (MSI1) and Musashi-2 (MSI2) due to an earlier duplication event in vertebrates. MSI1 and MSI2 share 75% amino acid identity and contain two RRM domains that facilitate target mRNA binding. MSI1 and MSI2 are found to play an important role in guiding the appropriate differentiation of neuronal progenitor cells (S. I. Sakakibara et al., 1996; S. Sakakibara, Nakamura, Satoh, & Okano, 2001) as well as in regulating organ development for other tissue types (Sutherland et al., 2014). The Musashi proteins have also been linked to cancer (Raymond G. Fox, Park, Koechlein, Kritzik, & Reya, 2015; Kudinov, Karanicolas, Golemis, & Bumber, 2017). For example, elevated expression of MSI1 was found in gliomas (Kanemura et al., 2001) and medulloblastomas (Dat T. Vo et al., 2012). In line with this, MSI1 overexpression correlates with poor prognosis in breast cancer patients (X. Y. Wang et al., 2010) and promotes the metastasis of breast cancer cells to lungs (Oskarsson et al., 2011). Additionally, MSI1 acts as a prognostic factor in ovarian (P. xiang Chen, Li, & Yang, 2015) and colorectal cancer patients (D. Li et al., 2011). Similarly, MSI2 is also found to play a role in cancer development. Msi2 was identified in chronic myeloid leukemia (CML) as part of a translocation event that fused the RRMs of Msi2 with HoxA9 (Barbouti et al., 2003). Using CML mouse model, Ito and colleagues showed that Msi2 regulates CML disease progression by binding and suppressing Numb mRNA (T. Ito et al., 2010). Another study showed that overexpression of Msi2 in BCR-ABL1 CML mouse model, led to induction of aggressive leukemia and thus, identified MSI2 as a prognostic marker for human AML (Kharas et al., 2010). Additionally, MSI2 has been shown to regulate growth and metastasis of pancreatic, lung, bladder and colon cancer (K. Guo et al., 2017; Kudinov et al., 2016; C. Yang et al., 2016; Zong et al., 2016). Together, these studies clearly indicate that the Musashi proteins are critical modulators of oncogenic initiation and progression.

### 3.5 HuR

HuR (Hu antigen R) is a member of ELAV family of RNA-binding proteins, which can associate with mRNAs containing AREs in their 3'-UTRs (Brennan & Steitz, 2001; Srikantan & Gorospe, 2012). HuR protein contains two tandem RNA-recognition motifs (RRM), a hinge region and a third RRM. The hinge region in HuR can be modulated by various kinases and is involved in nucleo-cytoplasmic shuttling of the protein. In response to

stress signals, such as UV irradiation and polyamine depletion, HuR is translocated from nucleus to cytosol wherein HuR binds to numerous target mRNAs and regulates their stability and/or translation (Kuwano et al., 2008; Lafarga et al., 2009; W. Wang et al., 2000; Xiaoling Yang et al., 2004; Zou et al., 2010). Additionally, HuR can directly bind to miRNAs and thus prevent the downregulation of their targets.

As the role of HuR in various cancers has been worked upon and reviewed extensively (Abdelmohsen & Gorospe, 2010; Brody & Dixon, 2018; J. Wang et al., 2013), we will discuss briefly about the function of HuR in different cancers (Also see Table 1). HuR is almost exclusively overexpressed in cancers. For example, HuR has been shown to be overexpressed in high-grade human brain tumors such as glioblastoma multiforme and medulloblastoma where it binds and stabilizes mRNAs of growth factors linked to brain tumor progression (Nabors, Gillespie, Harkins, & King, 2001). In addition, cytoplasmic expression of HuR in human breast tumors is associated with high tumor grade and poor disease-free survival (Heinonen et al., 2005). Similarly, cytoplasmic HuR correlates with increased colon cancer malignancy likely through its ability to stabilize  $\beta$ -catenin mRNA (López De Silanes et al., 2003). Moreover, over-expression of HuR is associated with advanced tumor grade in gastric cancer (Kang et al., 2008) and poor survival of HCC patients with early-stage disease (H. Zhu et al., 2015). Taken together, these data indicate that HuR is a critical RBP that promotes tumorigenesis and targeting HuR could be a useful cancer therapy.

#### 4. RBPS AS THERAPEUTIC TARGETS FOR CANCER

As evident from the above sections, RBPs not only play an indispensable role in normal physiology but also are vital to cancer initiation and progression. Thus, targeting RBPs for cancer therapy has gained more attention in the last decade. Recent years have seen increase in studies targeting the previously ‘undruggable’ RBPs as it has become increasingly possible to target these molecules using diverse approaches. In this section, we will review various strategies that have been used in recent years to target RBPs in cancer and other human diseases and also discuss some potential novel targeting schemes (Figure 2).

##### 4.1. Small molecules

Small molecules are by far the most commonly used compounds to target RBP function in cancers and other human diseases. Several of these molecules have shown promising anti-cancer activities in pre-clinical trials and some of them are currently being evaluated in clinical trials. Small-molecules can be used to inhibit RBP function in one of the following ways: 1) bind to the RBD and subsequently, impede RBP-RNA interaction; 2) disrupt interaction between RBP and its protein partner essential for its function in cancer; 3) prevent functional modifications of RBPs by inhibiting the activity of the enzymes involved; 4) modulate splicing of cancer causing genes by targeting core spliceosome machinery; 5) inhibit enzymatic activity of an RBP towards its target mRNA; 6) induce RBP degradation through targeting its E3 ubiquitin ligase. Here, we will provide a few examples for each strategy.

**4.1.1 Compounds targeting eIF4E**—The eukaryotic translation initiator factor 4E (eIF4E) is known to play an instrumental role in tumorigenesis and cancer progression and has been extensively studied as a target for cancer therapeutics. To date, several strategies have been applied to design small molecules that target eIF4E directly or indirectly for cancer management. The first approach is to target the binding of eIF4E to the cap structure. For example, ribavirin is a guanosine ribonucleoside analog that was initially found to mimic the cap structure and subsequently, compete with endogenous mRNAs for their binding with eIF4E (Kentsis, Topisirovic, Culjkovic, Shao, & Borden, 2004). Although the cap-binding mechanism of Ribavirin has been challenged by two different groups (Westman et al., 2005; Y. Yan, Svitkin, Lee, Bisailon, & Pelletier, 2005), it showed promising pre-clinical efficacy and also potent effect in clinical trials for AML and metastatic breast cancer (Assouline et al., 2009); however, it failed to show efficacy as a single agent in multiple antitumor screens involving xenograft models. Other cap-binding agonists include 4Ei-1 and Bn7-GMP (a synthetic nucleotide derivative that blocks the binding of eIF4E to the mRNA cap) (Ghosh et al., 2009; Jia et al., 2010), both of which are still under laboratory development stage and need to be further tested. Notably, 4Ei-1 has shown potent inhibition of cap-dependent translation both *in vitro* and *in vivo* in zebrafish embryos (Ghosh et al., 2009). More importantly, in combination with other drugs, 4Ei-1 has shown potent antitumor activities in breast, lung and mesothelioma cells (E. Z. Chen et al., 2014; S. Li et al., 2013). The second approach is to target the interaction between eIF4E and eIF4G, which is known to be critical for cap-dependent translation (Martineau, Azar, Bousquet, & Pyronnet, 2013; J. D. Richter & Sonenberg, 2005). Thus, several small molecules are designed to disrupt the interaction between eIF4E and eIF4G, including 4EGI-1, 4E1RCat, and 4E2RCat (Cencic, Desforges, et al., 2011; Cencic, Hall, et al., 2011; Moerke et al., 2007). All these compounds have shown cogent anti-tumor effects on cancer cells *in vitro*, breast cancer xenograft models *in vivo* and reverted chemoresistance in MYC-driven murine lymphoma models (Cencic, Hall, et al., 2011; Moerke et al., 2007). In addition to above compounds, two more eIF4E–eIF4G inhibitors were developed, including ouabain and perillyl alcohol (Cao et al., 2014; Peffley, Sharma, Hentosh, & Buechler, 2007). Ouabain is a cardiac glycoside and can disrupt eIF4E/eIF4G association in a panel of human cancer cells (Cao et al., 2014). Perillyl alcohol is a naturally occurring monoterpene and was found to attenuate interactions between eIF4E and eIF4G in prostate cancer cells (Peffley et al., 2007). The third approach is to sequester eIF4E by modulating the activity of 4E-BP, which is known to inhibit translation initiation by competing with eIF4G for a common binding site on eIF4E. As 4EBPs are direct substrates of mTOR kinase, targeting mTOR signaling pathway is a therapeutically attractive option for the purpose of sequestering eIF4E. mTOR kinase activity inhibition by small-molecule inhibitors has shown strong anti-cancer activities. Although the first generation of mTOR inhibitors (Rapamycin, RAD001, and CCI-779) showed potential efficacy in preclinical trials, they performed poorly in clinical trials against various human cancers due to poor inhibition of 4EBP phosphorylation (Hsieh & Ruggero, 2010). Next generation of potent mTOR inhibitors such as PP242, Ku-0083784, Torin1, Palomid 529, WYE-132, and AZD8055 function as ATP-active site inhibitors on mTOR and have shown more strong inhibition of phosphorylation of all mTOR targets including 4EBPs (Chresta et al., 2010; Feldman et al., 2009; García-Martínez et al., 2009; Thoreen et al., 2009; Q. Xue et al., 2008; Yu et al., 2010). Many of these mTOR active site



inhibitors and their more potent derivatives are being currently tested in clinical trials and promise a cogent therapeutic potential. The fourth approach is to block eIF4E phosphorylation by Mnk1, which is known to be critical for oncogenic activity of eIF4E (Topisirovic, Ruiz-Gutierrez, & Borden, 2004; Wendel et al., 2007). MNK inhibitors such as (5-(2-(phenylamino)pyrimidin-4-yl)thiazol-2(3H)-one derivatives, cercosporamide, and CGP57380 have shown significant inhibition of eIF4E phosphorylation and subsequent reduction in cancer cell proliferation by inducing apoptosis. Moreover, in animal models, cercosporamide treatment blocked eIF4E phosphorylation in normal and xenograft tissues, suppressed melanoma metastasis and decreased growth of AML xenografted tumors (Altman et al., 2013; Konicek et al., 2011). Most importantly, cercosporamide also suppressed colonization of freshly explanted AML patient samples (Altman et al., 2013).

**4.1.2 Compounds targeting the DEAD/H box RNA helicases**—The DEAD/H box RNA helicases, such as eIF4A (also called DDX2) and DDX3, are known to modulate translation of many oncogenes and thus, are being explored as targets for cancer management. Several small molecules have been developed to target this protein family by affecting the RNA binding and helicase activity or by disrupting specific protein-protein interactions (Bhat et al., 2015; Cai et al., 2017). For example, the activity of eIF4A can be blocked by several natural compounds, including silvestrol, pateamine A, and hippuristanol. All these compounds have shown potent growth inhibition in various human cancer cell lines and in mouse xenograft models and are currently being tested at pre-clinical stage (Alachkar et al., 2013; Chu et al., 2016; Iwasaki, Floor, & Ingolia, 2016; Iwasaki et al., 2019; S. Kim et al., 2007; Kuznetsov et al., 2009; Tsumuraya et al., 2011; Wolfe et al., 2014). Both silvestrol and pateamine A act as chemical inducers to stimulate eIF4A:RNA binding, which subsequently, sequesters eIF4A and inhibits the incorporation of eIF4A into the eIF4F translation initiation complex (Bordeleau, Cencic, et al., 2006; Bordeleau et al., 2008). Unlike silvestrol and pateamine A, hippuristanol prevents free eIF4A and eIF4F-bound eIF4A from interacting with RNA and thereby, inhibits translation initiation (Bordeleau, Mori, et al., 2006). Additionally, another compound, elatol was identified as a potent inhibitor of eIF4A with in vivo antitumor activity (Peters et al., 2018). Elatol specifically inhibits eIF4A helicase activity and shows no activity against other tested ATP-hydrolyzing enzymes, including other DEAD box helicases, or kinases (Peters et al., 2018).

In addition to eIF4A, RNA helicase DDX3 was found to be an attractive target for cancer therapeutic as it promotes tumor cell proliferation (Bol, Xie, & Raman, 2015). Several compounds have been discovered to inhibit either its helicase or ATPase activity. For example, RK-33 was found to specifically bind to DDX3 and abrogate its helicase activity (Kondaskar et al., 2010). Importantly, both RK-33 and nanoparticle formation of RK-33 was found to significantly inhibit tumor growth in multiple mouse models of lung cancer (Bol, Khan, et al., 2015; Bol, Xie, et al., 2015). In addition, several ring-expanded nucleoside analogues were found to target the RNA binding site of the human DEAD-Box RNA helicase DDX3 (Radi et al., 2012). However, further studies are needed to test whether these compounds have antitumor activity. More recently, drugs targeting the helicase Brr2 have been identified (M. Ito et al., 2017; Iwatani-Yoshihara et al., 2017); however, their antitumor efficacy is yet to be determined.



**4.1.3 Compounds targeting HuR**—As the most extensively studied RBP in cancer, HuR (Hu antigen R) is found to be aberrantly expressed in many types of tumor and is a promising target for cancer therapeutics. In 2007, Meisner et al discovered the first small molecular inhibitors, MS-444, dehydromutactin and okicenone, which interfere with the RNA binding activity of HuR (Meisner et al., 2007). Among these three inhibitors, MS-444 was the most potent and inhibited binding of HuR to target AREs by interfering with HuR dimerization. Further work with this compound demonstrated both *in vitro* and *in vivo* antitumor activity against colorectal cancer, reverted TRAIL resistance in pancreatic cancer and reduced glioma cell survival by inhibiting HuR multimerization (Blanco et al., 2016; Filippova et al., 2017; Lang et al., 2017; Romeo et al., 2016). In addition, two chemical compounds, quercetin and b-40, were identified by their ability to inhibit the formation of HuR:ARE (TNF- $\alpha$ ) complex and thereby, decrease TNF $\alpha$  mRNA stability and secreted TNF $\alpha$  (Chae et al., 2009; D'Agostino, Adami, & Provenzani, 2013). Nevertheless, the anti-tumor activities of these compounds need to be further tested as they function as anti-inflammatory agents (C. Guo, Yang, Jang, Zhou, & Liu, 2017). More recently, Wu et al reported that small molecule CMLD2 disrupts the interaction between HuR protein and its target mRNA, such as musashi (Xiaoqing Wu et al., 2015). CMLD-2 is a coumarin-derived molecule that was identified through high throughput screening of a library of 6,000 compounds developed by the Kansas University Chemical Methodologies and Library Development (CMLD) center. Later studies indicate that CMLD-2 exhibits cytotoxicity in a panel of cancer cell lines (R Muralidharan et al., 2017).

**4.1.4 Compounds targeting Musashi proteins**—Musashi proteins (MSI1 and MSI2) that are consistently over-expressed in a majority of the cancers also make an important target for therapy (Kudinov et al., 2017). Various groups have used high throughput screening assays to identify compounds that block the binding of Musashi proteins to its target RNAs. Using fluorescence polarization assay, Clingman et al. identified naturally occurring molecule oleic acid as the most potent inhibitor of Musashi binding to RNAs from two small molecule libraries that together consisted of more than 31000 compounds (Clingman et al., 2014). Oleic acid bound to the RRM1 of Musashi proteins and induced a conformational change that inhibited its binding to the target mRNA. Oleic acid was also shown to inhibit proliferation of MSI1 containing cells and provided a potential feedback loop between MSI1 activity and fatty acid biosynthesis which could be further studied and exploited to target MSI1 protein (Clingman et al., 2014). Using a smaller library, another group simultaneously identified three compounds that could inhibit Musashi association to RNA and these compounds had low IC50 (Minuesa et al., 2014). Although these compounds inhibit Musashi-RNA interaction, their effect on cell viability and proliferation has not been explored yet. Yet another group used RRM1 of MSI1 to screen for compounds that included FDA approved anti-cancer drugs and natural products. They identified the natural compound (–)-gossypol derived from cottonseed as their top hit with Ki in the nanomolar range (Lan et al., 2015). (–)-gossypol is known to have potent anti-tumor activity and has been used in several clinical trials targeting prostate cancer, NSCLC, glioblastoma, adenocortical carcinoma, CLL and other cancers either alone or in combination with other drugs.

**4.1.5 Compounds targeting other RBPs**—In addition to above mentioned compounds, several other compounds were also developed to target various RBPs. The RBP Lin28 regulates the maturation of the let-7 family of tumor-suppressor microRNAs by interacting with let-7 precursors through its two distinct cold shock and zinc-knuckle domains. Recently, two different groups discovered small-molecules that inhibit LIN28 binding to let-7 precursors. The first group utilized a protein/RNA FRET assay to screen for 16000 molecules and identified a molecule N-methyl-N-[3-(3-methyl[1,2,4]triazolo[4,3-b]-pyridazin-6-yl)phenyl] acetamide (referred to as 1632) that blocked the Lin28/let-7 interaction. This compound showed increased processed let-7, induced differentiation in embryonic stem cells and exhibited promising anti-tumor activities on cancer cells (Roos et al., 2016). Furthermore, Wang and colleagues used fluorescence polarization-based high throughput screen and identified two compounds that selectively blocked the LIN28-mediated let-7 processing (L Wang et al., 2018). Specifically, compound TPEN acts as a potent inhibitor of the zinc-knuckle domain of LIN28, while compound LI71 inhibits LIN28-mediated oligouridylation by interacting with the cold shock domain of LIN28. Furthermore, they showed that LI71 suppresses LIN28 in leukemia cells and embryonic stem cells. However, neither of the studies examined the effect of LIN28 inhibition on normal or cancer cell proliferation. A recent study showed that compound 1632 can inhibit cancer cell proliferation only at higher doses (Yanlian Chen et al., 2019). Moreover, compound 1632 reduced tumor xenografts in mice without affecting the body weight, indicating cancer specific effect of LIN28 inhibition.

Another recent study has identified Sam68 as a very potent target of ICG-001/CWP family of anti-tumor drugs. The authors for the first time demonstrated the role of Sam68 as a specific regulator of cancer stem cells compared to normal stem cells (Benoit et al., 2017). Sam68 was shown to be specifically overexpressed in colon, blood and breast cancer stem cells. The CWP drugs selectively inhibited self-renewal potential of patient derived leukemia stem cells as compared to healthy hematopoietic stem cells by inducing a complex formation between Sam68 and CBP leading to inhibition of the Wnt signaling pathway. More importantly, the Sam68/CBP complex formation was only induced by the drug in the cancer stem cells, thus providing specificity for killing cancer cells.

More recently, a novel approach of targeting RBPs in cancer was discovered serendipitously. Although anticancer sulfonamides such as indisulam have been used in clinical trials to treat advanced stage solid tumors, their mechanism of action was not known. Two recent studies demonstrated that indisulam increased the affinity of the E3 ubiquitin ligase DCAF15 for its substrate RBM39, resulting in the degradation of RBM39 in cancers and subsequent killing of cancer cells (T. Han et al., 2017; Uehara et al., 2017). Importantly, the treatment efficacy of indisulam was dependent on the levels of DCAF15 in patient tumors. Although indisulam has already shown modest efficacy in clinical trials of patients with metastatic disease, this compound did not advance because of its limited efficacy of response in about 10% of patients. Based on the finding that indisulam efficacy is proportional to DCAF15 expression in tumors, future clinical trials can focus on tumors expressing high levels of DCAF15 such as leukemia and lymphomas.

## 4.2 Oligonucleotide-based strategy

**4.2.1 Antisense oligonucleotides (ASOs)**—Antisense oligonucleotides (ASOs) are short (15–30bp), single stranded DNA analogs designed to bind to RNA by Watson-Crick base pairing. Upon binding to their target mRNAs, lncRNAs or miRNAs, ASOs perturb protein production by enhancing degradation of the targeted RNA (through RNaseH mediated degradation), altering RNA metabolism, or up-regulating gene expression. Being single stranded molecules, ASOs are very unstable and often need chemical modifications for stabilization. The benefit of ASOs include broad distribution and long-lasting effects. To date, six ASO drugs have been approved for the treatment of diseases such as viral infections, hyperlipidemias, and neurological diseases (Stein & Castanotto, 2017). Notably, several ASOs targeting RBPs have been designed for the treatment of neurodegenerative disorders. For example, spinal muscular atrophy (SMA) is a neurodegenerative disorder characterized by progressive loss of motor neurons, which is caused by loss or mutation of SMN1, an RBP involved in spliceosome. Interestingly, SMA patients carry a normal copy of SMN2, which is nearly identical to SMN1. However, the majority SMN2 gene products are truncated isoform excluding exon 7. Thus, an ASO, Nusinersen, was designed to prevent exon 7 exclusion by blocking the intronic splicing silencer (ISS) element in SMN2, resulting in the expression of the functional, full-length survival motor neuron protein from SMN2. In preclinical studies, Nusinersen was found to increase SMN2 levels and improved survival and neuromuscular function in SMA mice (Y. Hua et al., 2010, 2011; Rigo, Hua, Krainer, & Bennett, 2012). In December 2016, it became the first FDA approved drug for the treatment of SMA patients (Chiriboga et al., 2016; Mercuri et al., 2018). In addition to Nusinersen, ASO-based therapies are currently being tested to prevent RBP aggregation or alleviate RBP sequestration by repeat expansion in several neurodegenerative disorders (Nussbacher, Tabet, Yeo, & Lagier-Tourenne, 2019). Although there are no approved ASO drugs for cancer treatment, many attempts are being made. Indeed, ASOs against RBPs are being tested clinically and preclinically. For example, ASO against eIF4E [LY2275796] has been developed and has completed a phase I clinical trial (Hong et al., 2011). Phase II clinical trials are now under way combining ISIS EIF4E Rx with carboplatin and paclitaxel for non-small cell lung cancer (NCT01234038) or with docetaxel and prednisone for castration-resistant prostate cancer (NCT01234025). Similarly, another eIF4E ASO, ISIS 183750, showed significant tumor suppression in a mouse model and has also been tested in phase I/II clinical trials in patients with advanced colorectal cancer (Duffy et al., 2016). Additionally, ASO against Musashi was recently developed and found to effectively block tumor growth in preclinical models of pancreatic cancer (R G Fox et al., 2016). Interestingly, ASOs against Hu family proteins were also developed; however, they have not been tested for antitumor activities. To this end, ASO depletion of HuD via intrathecal injection reverts persistent pain in an animal model of antiretroviral therapy (Sanna, Peroni, Quattrone, Ghelardini, & Galeotti, 2015). Similarly, intrathecal ASO depletion of HuR attenuates mechanical allodynia in a model of autoimmune encephalomyelitis (Sanna, Quattrone, & Galeotti, 2017). Additionally, CPEB ASO treatment reduced hyperalgesic response to PGE2 or mechanical allodynia in rats (Bogen, Alessandri-Haber, Chu, Gear, & Levine, 2012; Iida et al., 2016).

**4.2.2 siRNAs**—Targeted delivery of small interfering RNA (siRNA)-nanoparticles for cancer treatment was first reported in 2010 and laid a solid foundation for RNA interference therapy (Davis et al., 2010). After almost two decades of research, siRNA-based therapies have demonstrated the efficacy and clinical safety and represent one of the more clinically advanced platforms for RNA drugs (Chi, Gatti, & Papoian, 2017). In 2018, FDA approved the first siRNA-based drug, Onpatro® as treatment for symptoms of peripheral nerve disease (polyneuropathy), caused by hereditary transthyretin amyloidosis in adult patients (W. Yin & Rogge, 2019). Notably, siRNA-based therapies have also been applied to target RBPs and have shown good promise in pre-clinical studies. For example, HuR has been recognized as a potential molecular target for RNAi therapy in several types of cancers such as NSCLC and ovarian cancer (Amreddy et al., 2018; Y. H. Huang et al., 2016). HuR siRNA has been tested for its efficacy to target various cancers via different target delivery methods. For example, HuR-targeted siRNA greatly reduced HuR expression and significantly inhibited the cell proliferation in lung cancer cells but not in normal cells (Amreddy et al., 2018). To achieve targeted delivery, a folate-conjugated nanoparticle system was developed recently and showed that silencing HuR suppresses lung cancer cell proliferation and migration. The rationale to use folate-conjugated nanoparticle was to reduce non-specific toxicity to normal cells and increase the therapeutic efficacy against tumor cells as majority of cancer therapies that are currently available are limited by cytotoxicity to normal tissues (Amreddy et al., 2018). More recently, another liposome nanoparticle delivery system was developed by using transferrin as a targeting ligand and showed to reduce the tumor burden in mouse models of lung cancer (Ranganayaki Muralidharan et al., 2017). Importantly, this therapy was also able to reduce the metastasis in A549 based metastasis mouse model compared to control siRNA-based nanoparticles. Additionally, HuR targeting by siRNA has been shown to impair malignant characteristics of pancreatic ductal adenocarcinoma cells (Jimbo et al., 2015). Moreover, HuR silencing sensitizes triple negative breast cancer cells to radiotherapy due to induction of oxidative stress and DNA damage (Mehta et al., 2016). Furthermore, conjugation of siRNAs against HuR with Cy3-labeled folic acid-coated DNA dendrimer nanocarrier has shown dramatic anti-oncogenic activity in ovarian cancer (Y. H. Huang et al., 2016). In addition to HuR, siRNAs against eIF4E have also been tested for their efficacy in multiple tumors. For example, a tumor-specific siRNA against eIF4E showed potent tumor suppression and enhanced cisplatin cytotoxicity in human breast carcinoma cells (Dong et al., 2009). Additionally, siRNAs against Musashi were found to inhibit growth of a panel of cancer cells in vivo and in vitro (H. Chen et al., 2019; Sheng et al., 2016; Sureban et al., 2008).

#### 4.4. Aptamers

Aptamers represent another strategy used for targeting RBPs in cancer, albeit less frequently. Aptamers can be either nucleic acid or peptide based and are selected on the basis of binding to a specific target (Mascini, Palchetti, & Tombelli, 2012). They fold into sequence specific three-dimensional structures that can recognize their unique target. They function similar to antibodies while also possessing several desirable properties such as smaller size, better stability and no immunogenicity (J. Zhou & Rossi, 2017). Nucleic acid aptamers consist of short, single-stranded DNA or RNA. Nucleic acid aptamers are selected using the procedure SELEX (systemic evolution of ligands by exponential enrichment), whereas peptide

aptamers are selected using yeast two hybrid technique, phage display, mRNA display or other techniques (Mascini et al., 2012). The first and only aptamer approved by FDA is the anti-VEGF aptamer pegaptanib (Macugen®; Pfizer/Eyetech) for treatment of macular degeneration in 2004. Although initially designed for use in cancer treatment, it did not show efficacy in pre-clinical studies and hence has not been tested in a clinical trial for cancer. While several aptamers are in the development stages as anti-cancer agents, only two therapeutic aptamers have made it to clinical trials for the treatment of cancer (Morita, Leslie, Kameyama, Volk, & Tanaka, 2018). One of them is the aptamer AS1411 (previously called AGRO100) against the RBP nucleolin and it was the first aptamer in clinical trial for cancer treatment. Nucleolin regulates several essential cellular processes including regulation of RNA polymerase I transcription, maturation and proper folding of the pre-ribosomal RNA, mRNA translation, mRNA stability and is overexpressed in cancers (Berger, Gaume, & Bouvet, 2015). AS1411, is a 26-nucleotide DNA based aptamer that forms stable G-quadruplex structures which are resistant to nucleases. AS1411 binds to the external domain of nucleolin and has shown growth inhibition in vitro and in vivo xenograft models of breast, lung and renal cancers (Ireson & Kelland, 2006). More importantly, AS1411 has been assessed in clinical trials for safety and efficacy in advanced solid tumors (NCT00881244) and renal cell carcinoma (NCT00740441). In its initial dose-escalation phase I clinical study, the administered doses of AS1411 were well tolerated and did not show any serious side effects. Based on these results, a Phase II trial was performed in patients with refractory metastatic renal cell carcinoma, but it showed limited efficacy in unselected patients implying the need for the discovery of AS1411 responsive biomarkers in tumors. Yet another Phase II clinical trial assessed the efficacy of AS1411 in combination with anti-cancer drug cytarabine in relapsed or refractory AML patients (NCT00512083). This study found improved response rates in patients receiving the combination therapy compared to the cytarabine alone group, indicating anti-tumor effect of AS1411 in AML. In addition to nucleolin, aptamers have also been developed against the DEAD-box RNA helicase eIF4A, the RNA editing enzyme ADAR1 and the dsRNA-dependent protein kinase PKR that inhibit their helicase activity, RNA editing or dsRNA binding ability, respectively (Hallegger, Taschner, & Jantsch, 2006; Oguro, Ohtsu, Svitkin, Sonenberg, & Nakamura, 2003; Zheng & Bevilacqua, 2004). Although these aptamers have not been used as anti-cancer agents in clinical trials, based on the promising clinical efficacy of AS1411, there remains a potential for the development of these and other RBP-based aptamers for anti-cancer therapeutics.

#### 4.5 Peptides

Therapeutic peptides are receiving increasing attention for biomedical applications. Peptides present promising opportunities in targeted drug delivery due to their high specificity, selectivity, small dimension, ease of modification, and high biocompatibility. During the last decade, the potential of peptides as therapeutics or targeting ligands has boomed in nanotechnology and cancer research. There are several types of peptides being developed for cancer treatment (Marqus, Pirogova, & Piva, 2017) and some of these peptide are designed to target RBPs. For example, Yo and colleagues developed several 4EBP-based peptides that bound eIF4E and subsequently, disrupted the interaction of eIF4E to eIF4G, leading to inhibited cap-dependent translation (Y. K. Song, Guo, Barengo, & Naora, 2009). Notably,



when fused with gonadotropin-releasing hormone agonist, these peptides exerted potent antitumor effects in a mouse xenograft model of epithelial ovarian cancer without eliciting significant toxicity. Recently, we also developed a small peptide that can inhibit tumor growth in vitro and in vivo (Lucchesi, Zhang, Ma, Chen, & Chen, 2019). The rationale is based on our previous finding that RBM38 inhibits p53 mRNA translation by preventing the binding of eIF4E to the p53 mRNA (J Zhang et al., 2011). Thus, we designed synthetic peptides corresponding to the binding interface between RBM38 and eIF4E and showed that the peptides were effective in relieving RBM38-mediated repression of p53 translation. Notably, we showed that this peptide alone or together with a low dose of doxorubicin potently induced p53 expression and suppressed colony formation, tumor sphere formation and xenograft tumors in RBM38- and p53-dependent manners.

#### 4.6 Other potential strategies to target RBPs in cancer

**4.6.1 Circular RNAs (circRNAs)**—Circular RNAs are naturally occurring covalently closed circle RNAs found in majority of eukaryotic cells that are formed by back-splicing of exons (Kristensen, Hansen, Venø, & Kjems, 2018). Although discovered 40 years ago, until recently they were considered the product of splicing errors (M. T. Hsu & Coca-Prados, 1979). Following recent studies that showed circRNAs are functional, conserved and that their formation is non-random (Hansen et al., 2013; Jeck et al., 2013; Memczak et al., 2013), there has been an explosion in studies describing the vital roles of circRNAs in normal physiology and disease. Several studies have described the role of circRNAs in cancer development. circRNAs function in cancers by acting as miRNA or RBP sponges, by regulating transcription and splicing, and can also undergo translation. Interestingly, one circRNA may contain several sites for a single or multiple RBPs and thus regulate the function of RBPs by acting as an RBP sponge or decoy (Kristensen et al., 2018). This phenomenon is observed in the binding of circRNAs derived from muscleblind (mbl) locus to MBL protein itself. The binding of circRNA inhibits MBL function by preventing its binding to its mRNA targets (Ashwal-Fluss et al., 2014). Another example of circRNAs acting as an RBP sponge comes from the binding of circRNA derived from PABPN1 gene to HuR. HuR has been shown to bind PABPN1 mRNA and increase its translation; however, binding of circPABPN1 to HuR prevents its binding to PABPN1 mRNA, resulting in decreased PABPN1 translation (Abdelmohsen et al., 2017). More importantly, sequestering of HuR by circPABPN1 may also affect other cancer relevant HuR targets such p53, c-myc and bcl-2. In addition to this, circRNAs are extremely stable and have a long half-life in cells. These properties of circRNAs make them a promising therapeutic strategy for targeting RBP functions in cancer. Natural or recombinant circRNAs capable of sequestering oncogenic RBPs can thus be used to treat cancers overexpressing the particular RBP. Although, there have been no preclinical reports that have utilized circRNAs sequestering RBPs as therapeutic molecules for cancer treatment, this is likely going to change in the near future.

**4.6.2 CRISPR based strategies**—In the past decade, the development of CRISPR/Cas9 system has shown potential therapeutic applications for the treatment of cancer. Several clinical trials are ongoing that are testing efficacy of CRISPR based therapy for cancer treatment. Majority of the clinical trials are immunotherapies that are targeting the



negative immune regulator protein program cell death 1 (PD-1) (X. Tian et al., 2019). In addition, several studies have utilized CRISPR based therapies for the treatment of human diseases including cancer in human patient cells. For example, a recent study utilized CRISPR to correct the autoimmune disease causing IL2RA mutation in human patients and showed promising results (Roth et al., 2018). The same study also used CRISPR to replace endogenous T-cell receptor with a new T-cell receptor that assisted T-cells towards cancer antigens (Roth et al., 2018). Another study showed that RNA-targeting CRISPR system induced specific degradation of microsatellite repeat expansion RNAs, caused by dysfunctional RNA splicing in various neurodegenerative disease bearing patient cells (Batra et al., 2017). Although CRISPR/Cas9 system has not yet been used to target RBPs for cancer therapy, the above studies provide a promising future for their use in cancer therapy. CRISPR can be used to directly target an RBP or its function by different means. For example, it can be used to knockout an oncogenic RBP in cancer cells, to correct cancer specific RBP mutations or modulate RBP binding sites in mRNAs that would lead to aberrant splicing of oncogenes. Similarly, they could be used to target immune-suppressive RBPs in immunotherapies in combination with checkpoint inhibitors. Thus, although not used for targeting RBPs in preclinical cancer studies yet, CRISPR represents an encouraging approach for developing RBP-targeted cancer therapies.

## 5. CONCLUSIONS AND FUTURE PERSPECTIVES

RBPs control multiple cancer traits by regulating several genes that form an intricate network and multitude of studies have shown an indisputable role for RBPs in tumorigenesis. Thus, RBPs are emerging as promising targets for cancer therapy. Of particular interest, recent studies suggest a role of RBPs in cancer immunotherapy. Cancer immunotherapy works by boosting patients own immune system to attack tumor cells by using immune checkpoint inhibitors (ICIs) (Topalian, Drake, & Pardoll, 2015). The ICIs usually target the inhibitory CTLA4 and PD1 receptors present on the T-cells or PD-L1 ligand present on tumor microenvironment immune cells or overexpressed on tumor cells. Although immunotherapy has shown promising clinical outcomes in several patients, some patients still fail to respond due to development of resistance (Jenkins, Barbie, & Flaherty, 2018). Interestingly, several RBPs have been involved in pathways that lead to immunotherapy resistance either by remodeling tumor cells to evade immune response or by working in immune cells to blunt the immune cell's efficacy to fight tumor cells. For example, the RBP MEX3B has been shown to destabilize HLA-A mRNA in tumor cells and mediate resistance to cancer immunotherapy (L. Huang et al., 2018). Similarly, the oncogenic RBP IMP3 (IGF2BP3) was shown to decrease stress-induced ligands ULBP2 and MCIB, leading to impaired recognition of transformed cells by NK cells (Schmiedel et al., 2016). In addition, ADAR1 plays a role in immune resistance by regulating the biogenesis of miR-222 and thereby ICAM1 protein expression (Galore-Haskel et al., 2015). Moreover, eIF4E has been recently shown to enhance the translation of PD-L1 in mouse tumors, which was abrogated by eFT508, the eIF4E phosphorylation inhibitor (Yichen Xu et al., 2019). Together, these studies suggest that RBPs are promising targets to increase the efficacy of immunotherapy in patients due to their role in immune suppression/evasion.

To date, only a few RBPs have been targeted for cancer therapy, by using various approaches, in preclinical and clinical studies. The major challenges include: (1) the delivery methods to target RBP in cancer need to be improved; (2) Selective targeting of cancer cells as most of the RBPs are required for the survival of both normal and cancer cells; (3) identify subsets of cancers that are highly dependent on a particular RBP for proliferation and survival; (4) the biological function of most RBPs in cancer has not been fully understood yet. For example, some RBPs work as tumor suppressors under one circumstance but as an oncogene under another circumstance. Additionally, it is in urgent need to identify critical targets of an RBP that mediate its cancer-related functions. To overcome these challenges, several strategies may be applied. For example, to develop targeted therapies that kill cancer cells, it will be important to design nanoparticle carriers for siRNA, ASOs, aptamers and peptides that recognize altered cancer-specific cell-surface markers and thus can be targeted specifically to cancer cells. Second, it will also be important to develop small molecules or peptides that inhibit the interaction of an RBP with only a subset of its targets that are cancer relevant. Third, it will be important to identify cancer-specific PTM(s) of an RBP and the kinase(s) involved in different cancer types. For example, phosphorylation of eIF4E specifically increases translation of oncogenic mRNAs and consistent with this, inhibition of eIF4E phosphorylation by small molecule inhibitors only affects the translation of oncogenic mRNAs in cancer without affecting normal cell proliferation. Fourth, the techniques such as PAR-CLIP, RIP-seq, iCLIP and others will prove valuable in defining the targets of an RBP or its interacting partners in cancer, which would lay a foundation for the development of novel cancer therapeutics. Finally, recent studies have revealed a critical role of non-canonical RBPs in regulating RNA metabolism and fate and have been implication in cancer. Thus, it is important to consider the role of these non-canonical RBPs and their cross talks with canonical RBPs. A key challenge here would be defining the targets of non-canonical RBPs in cancer as these cannot be predicted bioinformatically due to lack of available structure-function studies. In summary, considering that the number of RBPs whose functions are still not completely understood, our current knowledge about cancer-related RBPs seems to be the tip of the iceberg and reinforces the need for substantial work to be done in the future.

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## Abbreviations

<b>3'UTR</b>	3' untranslated region
<b>5'UTR</b>	5' untranslated region
<b>AML</b>	Acute myeloid leukemia
<b>ARE</b>	AU-rich element
<b>ASO</b>	Antisense oligonucleotide

<b>circRNAs</b>	Circular RNAs
<b>CML</b>	Chronic myeloid leukemia
<b>dsRBD</b>	Double-stranded RNA binding domain
<b>dsRNA</b>	Double-stranded RNA
<b>hnRNP</b>	heterogeneous nuclear ribonucleoprotein
<b>KH</b>	K-homology
<b>miRNAs</b>	MicroRNAs
<b>mRNAs</b>	Messenger RNAs
<b>PAZ</b>	Piwi/Argonaute/Zwille
<b>PCBP</b>	poly(C)-binding protein
<b>PIWI</b>	P-element Induced WImpy testis
<b>PUM</b>	Pumilio homology domain
<b>RBD</b>	RNA-binding domain
<b>RBP</b>	RNA-binding protein
<b>RNP</b>	Ribonucleoprotein
<b>RRM</b>	RNA recognition motif
<b>siRNA</b>	Small interfering RNA
<b>TTP</b>	Tristetraprolin
<b>UTR</b>	Untranslated region
<b>ZNF</b>	Zinc finger

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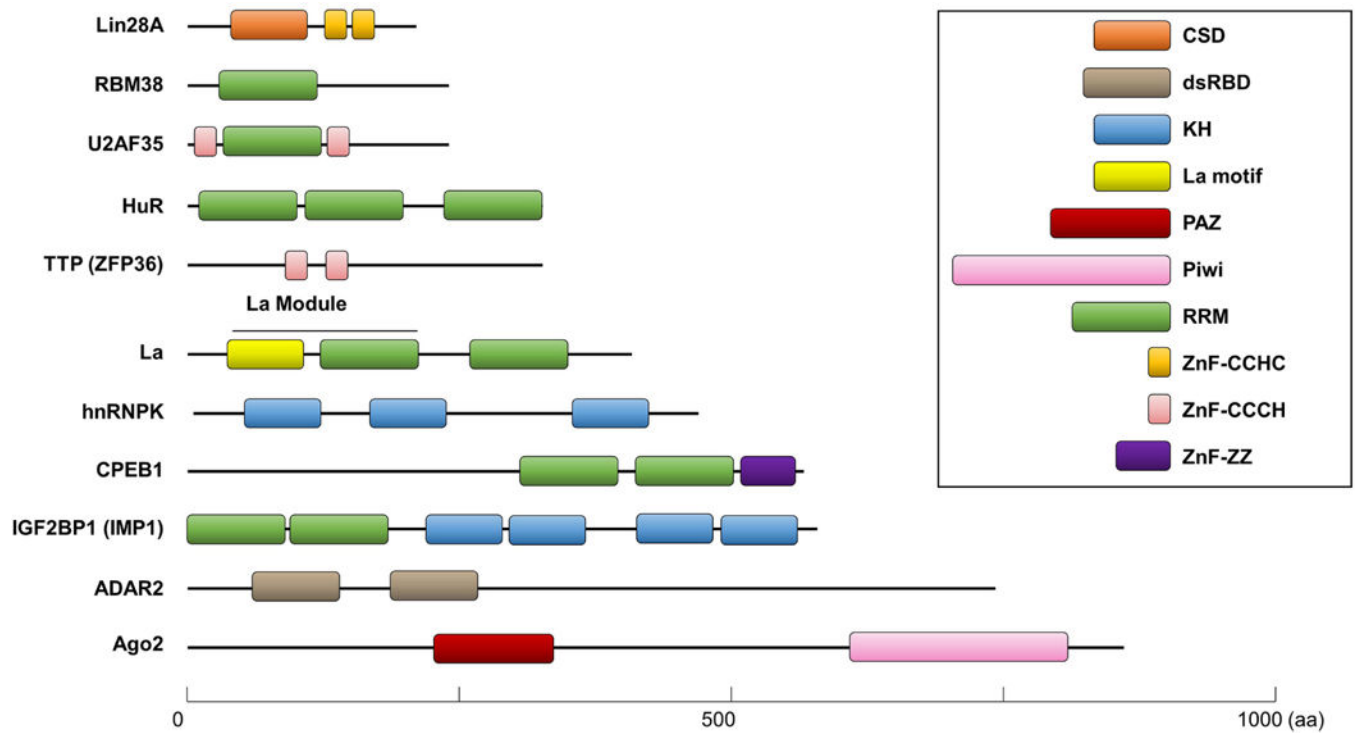
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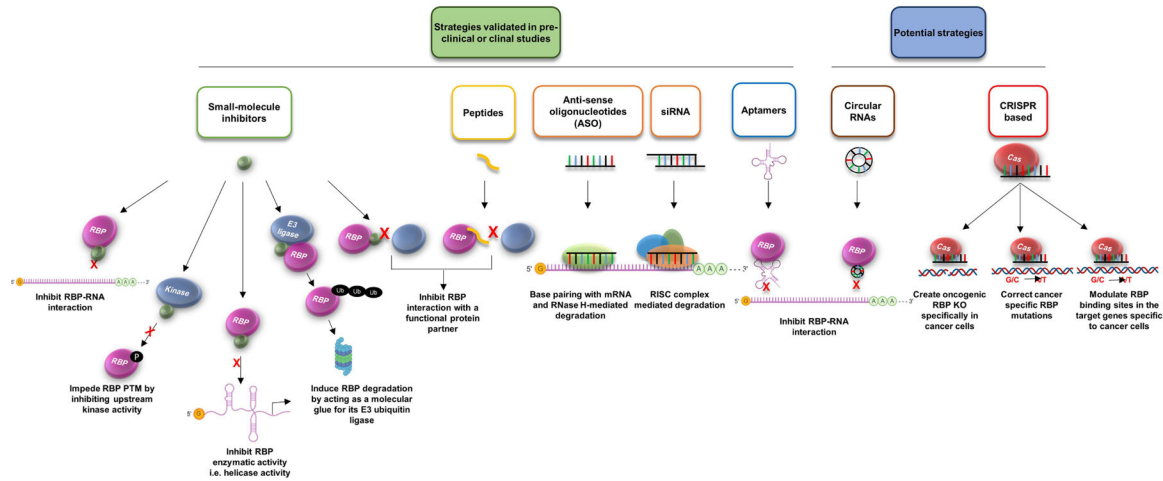
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**Figure 1.**

Schematic representation of RNA-binding proteins (RBPs) with various RNA-binding domains (RBDs). Each RBD is drawn as colored boxes and their lengths are shown according to their actual sizes (aa, amino acids). The common RBDs include: CSD, cold shock domain; dsRBD, double-stranded RNA-binding domain; KH, K-homology domain; La motif; PAZ, Piwi/Argonaute/Zwille domain; Piwi domain; RRM, RNA-recognition motif; ZnF, zinc fingers of the CCHC, CCCH, and ZZ type.



**Figure 2.** Strategies that are being applied to target RBPs for cancer therapeutics. Small-molecules can be designed to inhibit the interaction of RBP with an RNA, suppress RBP's enzymatic activity, block RBP post-translational modification (PTM), or induce RBP degradation. The Peptides-based strategy can be designed to hinder the RBP association with its functional partner(s). The oligonucleotide-based strategies include ASO, siRNA, and Aptamer, which can either mediate RBP mRNA degradation or inhibit RBP-RNA interaction. In addition, two potential strategies are included, natural or artificial circular RNAs- or CRISPR-based approaches. Circular RNAs can be designed to bind RBDs of RBPs and compete out target RNAs. CRISPR based approaches can be used to create oncogenic RBP knockout/knockin (to correct cancer-specific mutation in RBP or RBP binding sites). RISC, RNA-induced silencing complex.

Table-1–

Altered RBPs in cancer and the therapeutic strategy used (if any) to target them

RBD class	RBP gene symbol	RNA regulation mechanism	Cancer type regulated	Expression in cancers	Therapeutic strategy used (if any)	References
Cap-binding	eIF4E	mRNA translation	Breast, bladder, cervical, esophageal, gastric, head and neck, liver, lung, lymphoma, prostate,	Upregulated in cancers	Small molecules inhibiting cap binding, eIF4E phosphorylation, association with eIF4G, ASOs against eIF4E	(Bhat et al., 2015; C. N. Chen, Hsieh, Cheng, Lee, & Chang, 2004; Crew et al., 2002; Fan et al., 2009; Furic et al., 2010; Graff et al., 2009; Hsieh et al., 2010; B. D. Li, Mc Donald, Nassar, & De Benedetti, 1998; Modeliska et al., 2015; Naithan et al., 1999; Pelletier, Graff, Ruggiero, & Sonenberg, 2015; Rosenwald, Hutzler, Wang, Savas, & Fraire, 2001; Truitt et al., 2015; S. Wang et al., 1999; X. L. Wang, Cai, Ge, & Shi, 2012; Yichen Xu et al., 2019; Yoshizawa et al., 2010)
	eIF4A1 (DDX2A)	mRNA translation	Breast, cervical, endometrial, lung, leukemia	Upregulation linked to poor outcome	Small molecules targeting dimerization or helicase activity	(Bhat et al., 2015; Bordeleau, Mori, et al., 2006; Bordeleau et al., 2008; Chu et al., 2016; Comtesse et al., 2007; Ji et al., 2003; Liang et al., 2014; Lomnyska et al., 2012; Modeliska et al., 2015; Pelletier et al., 2015; Schatz et al., 2011; Wolfe et al., 2014)
DEAD-box helicase containing	eIF4AII (DDX2B)	mRNA translation	Breast, Lung	Upregulation linked to better survival	Small molecules targeting eIF4A1 can also inhibit eIF4AII	(Raza, Waldron, & Quesne, 2015; Shaoyan et al., 2013; L. X. Yan et al., 2011)
	DDX3	mRNA translation	Brain, breast, colon, head and neck, liver, lung, leukemia, prostate, sarcoma	Upregulated in breast, colon, liver, lung cancers and sarcoma but mutations in brain, head and neck and hematological cancers	Small-molecule inhibitor that binds to the ATP-binding pocket and inhibits RNA helicase activity	(Bol, Khan, et al., 2015; Bol, Vesuna, et al., 2015; Bol, Xie, et al., 2015; Bollagumta et al., 2008; Dunford et al., 2017; Heerma van Voss, van Diest, & Raman, 2017; Heerma Van Voss et al., 2018; J. S. Huang et al., 2004; L. Jiang et al., 2015; Y. Jiang et al., 2014; Pugh et al., 2012; J. Richter et al., 2012; Stransky et al., 2011; van Voss et al., 2015; Lili Wang et al., 2011; Wilky et al., 2016; Xie et al., 2016)
	DDX5 and DDX17	mRNA, rRNA, miRNA processing, alternative splicing	Brain, breast, colon, prostate, skin	Overexpression	NA	(Causevic et al., 2001; Clark et al., 2008; Mazurek et al., 2012; Shin, Rossow, Grande, & Janknecht, 2007; R. Wang, Jiao, Li, Yue, & Chen, 2012; S. J. Wang, Zhang, Yout, & Shi, 2012; Wortham et al., 2009)
	DDX6	mRNA translation	Brain, colon, gastric, liver	Upregulated in cancers	NA	(Akao et al., 1995; Baskin et al., 2015; Fuller-Pace, 2013; F. Lin et al., 2008; Miyaji et al., 2003; Nakagawa et al., 1999; Taniguchi et al., 2018)
dsRBD containing	ADAR1	RNA editing	Breast, colon, esophageal, gastric, liver, lung, leukemia, melanoma	Upregulated in most cancers; down-regulated in melanoma	NA	(Amin et al., 2017; Beghini et al., 2000; Chan et al., 2014, 2016; L. Chen et al., 2013; Fritzell, Xu, Lagergren, & Öhman, 2018; Fumagalli et al., 2015; Gu mireddy et al., 2016; L. Han et al., 2015; S.-W. Han et al., 2014; Nemlich et al., 2013; Paz-Yaacov et al., 2015; Peng et al., 2018; Shoshan et al., 2015)
	ADAR2	RNA editing	Brain, colon, esophageal, gastric, liver	Downregulated in most cancers	NA	(Conrati, Mian, & Bateman, 2000; Chan et al., 2014, 2016; Yuan Bin Chen et al., 2017; Fritzell et al., 2018; L. Fu et al., 2017; Galeano et al., 2013; Maas, Patt, Schrey, & Rich, 2002; Paz et al., 2007; Shelton et al., 2018)
KH-domain containing	hnRNPk	mRNA translation	Bladder, gastric, head and neck, leukemia, liver, melanoma, prostate	Upregulated or downregulated based on cancer	NA	(L. C. Chen et al., 2008; X. Chen et al., 2017; Enge et al., 2009; Ga llardo et al., 2015; L. Liu et al., 2018; Nagano et al., 2004; Wen et al., 2010; C. S. Wu et al., 2012; R. Yang et al., 2016)
	KHSRP	miRNA processing, mRNA stability, alternative splicing	Brain, breast, esophageal, liver, lung, renal, testis, thyroid	Upregulated or downregulated based on cancer type	NA	(Gou et al., 2018; Malz et al., 2009; Puppo et al., 2016; Tong et al., 2016; Trabucchi et al., 2009; Jian Yang et al., 2013; Xinna Zhang, Wan, Berger, He, & Liu, 2011)
	PCBP1 (hnrNPE1)	mRNA stability; mRNA translation	Breast, cervical, colon, leukemia, liver, lung, prostate	Down-regulated in cancers	NA	(J. Guo & Jia, 2018; Y. Liu et al., 2015; Pillat et al., 2003; Thakur et al., 2003; H. Wang et al., 2010; T. Zhang et al., 2010; Y. Zhang et al., 2018; M. Zhou & Tong, 2015)
	PCBP2	mRNA stability	Brain, breast, esophageal, gastric, liver	Up-regulated in most cancers	NA	(W. Han et al., 2013; Hu et al., 2014; F. Li et al., 2016; Luo & Zhuang, 2017; Ren et al., 2016; J Ye et al., 2016; X Zhang et al., 2016)
	PCBP3	mRNA stability	Pancreas	Down-regulated in cancers	NA	(Ger et al., 2018)
	PCBP4	mRNA stability	Head and neck, lung, lymphoma	Down-regulated in cancers	NA	(Castano et al., 2008; Y. Ito et al., 2015; Pio et al., 2004; W. Yan et al., 2016; J. Zhu & Chen, 2000)
	Sam68	Alternative splicing	Breast, leukemia, prostate, renal	Upregulated in cancers	Small molecule inhibitors increasing association with CBP	(Benoit et al., 2017; Bielli, Busà, Paronetto, & Sette, 2011; Buss et al., 2007; Cheung, Chan, Thompson, Cleary, & So, 2007; K. Fu et al., 2016; Mütter, Herrlich, & König, 2002; Paronetto et al., 2010; Richard et al., 2008; L. Song et al., 2010)

RBD class	RBP gene symbol	RNA regulation mechanism	Cancer type regulated	Expression in cancers	Therapeutic strategy used (if any)	References
La module containing	La	mRNA translation	Cervical, head and neck, liver, leukemia	Upregulated in cancers	NA	(Heise et al., 2016; Holcik & Korneluk, 2002; Marita, Martijssen, Cruz-Gallardo, & Conte, 2017; Nakatake et al., 2012; Pez, Them, Huber, Beig, & Mikutis, 2012; Sommer et al., 2011; Troita et al., 2003)
	LARP1	mRNA stability, mRNA translation	Cervical, colon, lung, ovarian, prostate	Upregulated in cancers	NA	(Burrows et al., 2010; Hopkins et al., 2016; M. Kato et al., 2015; Mura et al., 2015; Stavraka & Blagden, 2015; Teherkezi et al., 2014)
	LARP6	mRNA translation	Breast	Upregulated in breast cancer	Small molecule inhibitor	(Shao et al., 2012; Stavraka & Blagden, 2015; Stefanovic, Manojlovic, Vied, Badger, & Stefanovic, 2019)
	LARP4B	mRNA stability	Brain, breast, leukemia	Down-regulated in brain, breast; up-regulated in leukemia	NA	(Koso et al., 2016; Marita et al., 2017; Seetharaman, Flemmyng, Shen, Conte, & Ridley, 2016; Stavraka & Blagden, 2015; Yingchi Zhang et al., 2015)
	LARP7	snRNA stability	Breast, cervical, gastric	Down-regulated in cancers	NA	(Biewenga et al., 2008; Cheng et al., 2012; N. He et al., 2008; X. Ji, Lu, Zhou, & Luo, 2014)
	PUM1 and PUM2	mRNA translation	Bladder, breast, ovary	Down-regulated in cancers	NA	(Guan et al., 2018; Lee et al., 2016; Miles et al., 2016; Miles, Tschöp, Herr, Ji, & Dyson, 2012)
	TTP (ZFP36)	mRNA stability, mRNA translation	Brain, breast, colon, leukemia, liver, melanoma, pancreas, prostate	Upregulated or downregulated based on cancer type	NA	(Abba et al., 2007; Hodson et al., 2010; Milke et al., 2013; Park et al., 2018; Shimada et al., 2000; Wei et al., 2016; Zindy et al., 2006)
Zinc finger containing	ESRP1	Alternative splicing	Breast, colon, head and neck, lung, melanoma, ovarian, pancreatic, prostate, renal	Upregulated or downregulated based on cancer type	NA	(Fagocnee et al., 2016; Ge rhauser et al., 2018; Guha et al., 2018; Hayakawa, Satoh, & Miyazawa, 2017; Ishii et al., 2014; Jeong et al., 2017; Larsen et al., 2016; Leonieva & Ionov, 2009; H. Lu et al., 2013; Precu et al., 2015; Ueda et al., 2014; Warzecha et al., 2010; Yae et al., 2012; Yao et al., 2016; H. Zhang et al., 2019; Q. Zhao et al., 2015)
	ESRP2	Alternative splicing	Breast, colon, head and neck cancer, renal	Upregulated or downregulated based on cancer type	NA	(Deloria et al., 2016; Mizutani, Koizumi, Seimiya, & Miyazono, 2016; Shapiro et al., 2011; Warzecha, Sato, Nabet, Hogenesch, & Carstens, 2009)
	HuR	mRNA translation, mRNA stability	Bladder, brain, breast, cervical, colon, gastric, liver, leukemia, ovarian, pancreatic, prostate, renal	Upregulated in most cancers	Small molecule inhibitors, targeted delivery of siRNA by nanoparticles	(Abdelmohsen & Gonospe, 2010; Brody & Dixon, 2018; X. Guo, Wu, & Hartley, 2009; Ishimaru et al., 2009; Kang et al., 2008; López De Silanes et al., 2003; Meisner et al., 2007; Ranganayaki Muraidharan et al., 2017; Nabors et al., 2001; Vázquez-Chantada et al., 2010; A. Wang et al., 2019; J. Wang et al., 2013; Xiaoxing Wu et al., 2015; H. Zhu et al., 2015)
	MSH1 and MS12	mRNA translation, mRNA stability	Bladder, brain, breast, colon, endometrial, gastric, leukemia, liver, lung, ovarian, pancreatic	Upregulated in cancers	Small molecules inhibiting association with target mRNAs	(Clingman et al., 2014; Raymond G. Fox et al., 2015; K. Guo et al., 2017; L. He et al., 2014; Kudimov et al., 2017; Lan et al., 2015; D. Li et al., 2011; Minnesa et al., 2014; D. T. Vo et al., 2012; C. Yang et al., 2016)
	RBM9 (Rbfox2)	Alternative splicing	Breast, colon, ovary	Down-regulated in cancers	NA	(Braeutgam et al., 2014; S. Choi, Sa, Cho, Kim, & Park, 2019; J. P. Venables et al., 2012; Julian P. Venables et al., 2009)
	RBM10	Alternative splicing	Lung, pancreas, thyroid	Down-regulated or mutated in cancers	NA	(Bachara, Sebestyén, Bernardis, Eyras, & Va lcarcel, 2013; Hernández et al., 2016; Ibrahimspasic et al., 2017; Witkiewicz et al., 2015; J. Zhao et al., 2017)
	RBM24	mRNA translation, alternative splicing, mRNA stability	Breast, Head and neck	Down-regulated in cancers	NA	(W. F. Hua et al., 2016; Z. L. Wang et al., 2018)
RRM containing	RBM38	mRNA translation, alternative splicing, mRNA stability	Breast, colon, liver, lymphoma, renal	Upregulated or downregulated based on cancer type	Peptide inhibiting interaction with eIF4E	(W. Huang et al., 2017; Leveille et al., 2011; Lucchesi et al., 2019; Wampfler, Federzoni, Torbett, Fey, & Tscham, 2016; J. Q. Xue et al., 2014; Jiazhou Ye et al., 2018; J Zhang et al., 2011, 2014, 2018)
	RBM39	Alternative splicing	AML, Breast, Colon	Upregulated in AML, breast cancer	Small molecules enhancing RBM39 degradation by DCAF15	(T. Han et al., 2017; Mercier et al., 2009; Sillars-Hardebol et al., 2012; Uehara et al., 2017; E. Wang et al., 2019)
	RBM47	Alternative splicing	Breast, colon, lung	Down-regulated in cancers	NA	(Budinska et al., 2013; Rokavec, Kailer, Horst, & Hermeking, 2017; Sakurai et al., 2017; Vanharanta et al., 2014)
	hnRNPA1/A2	Alternative splicing	Brain, breast, colon, liver, lung, pancreas	Upregulated in cancers	NA	(Boukakis, Patrino-Georgoula, Iekarakou, Vajavakis, & Gi ialis, 2010; Clower et al., 2010; David, Chen, Assamah, Canoll, & Manley, 2010; Go lan-Gerstl et al., 2011; Parry et al., 2003; Tauter, Zhdarec, Liu, Shih, & Mulshine, 2010; Ushigome et al., 2005; Z. J. Zhou et al., 2015)
	hnRNPD (AUF1)	mRNA stability, mRNA translation	Breast, colon, gastric, liver, lung, pancreas, renal, sarcoma, thyroid	Upregulated in most cancers	NA	(Abdelmohsen et al., 2012; Blaxall et al., 2000; Gouble et al., 2002; J. Li, He, Xu, & Huang, 2019; Trojanowicz et al., 2009; Vázquez-Chantada et al., 2010; Xia Wu et al., 2018; Zucconi, 2011)
	hnRNPM	Alternative splicing	Breast	Upregulated	NA	(Harvey et al., 2018; Yilin Xu et al., 2014; F. L. Zhang et al., 2018)
	Continued					

RBD class	RBP gene symbol	RNA regulation mechanism	Cancer type regulated	Expression in cancers	Therapeutic strategy used (if any)	References
<b>RRM and KH domain containing</b>	IGF2BP1 (IMP1)	miRNA localization, mRNA stability, mRNA translation	Breast, colon, lung, melanoma, ovary, skin	Upregulated in cancers	NA	(Doyle, Bourdeau-heller, Couillard, Meisner, & Ross, 2000; Ghoshal et al., 2019; Gu, Pan, & Singer, 2009; Hüttelmaier et al., 2005; Ioannidis et al., 2003, 2001; T. Kato et al., 2007; Zhenqun Liu et al., 2018; Mongroo et al., 2011; Müller et al., 2018; Ross, Lemm, & Berberet, 2001)
	IGF2BP2 (IMP2)	miRNA localization, mRNA stability	Brain, breast, leukemia, lung	Upregulated in cancers	NA	(Degrauwe et al., 2016; X. He et al., 2018; R. sheng Huang et al., 2018; Janiszewska et al., 2012; McMullen et al., 2018)
	IGF2BP3 (IMP3)	miRNA stability, mRNA translation	Breast, colon, leukemia, lung, ovary, pancreas, renal	Upregulated in cancers	NA	(K. F. Hsu et al., 2015; Jønsson et al., 2014; Palanichamy et al., 2016; Samanta et al., 2018; Senoo et al., 2018)
<b>RRM and Zinc finger containing</b>	CPEB1	Alternative splicing, mRNA translation, polyadenylation	Breast, liver	Upregulated in cancers	NA	(Bava et al., 2013; Calderone et al., 2016; D' Ambrogio, Nagaoka, & Richter, 2013; Nagaoka et al., 2016; M. Xu et al., 2018)
	CPEB4	miRNA translation, polyadenylation	Brain, liver, melanoma, pancreas	Upregulated in cancers	NA	(Calderone et al., 2016; D' Ambrogio et al., 2013; Ortiz-Zapater et al., 2012; Pérez-Guijja et al., 2016)
	RBM4	Alternative splicing	Breast, colon, gastric, liver, lung, pancreas, ovary	Down-regulated in cancers	NA	(J. Y. Chen, Liu, & Xu, 2017; J. C. Lin et al., 2017; Y. Wang et al., 2014; Yong et al., 2016)
<b>CSD and Zinc finger containing</b>	LIN28A and LIN28B	miRNA processing, miRNA translation	Brain, breast, colon, cervical esophageal, head and neck, liver, lung, lymphoma, renal, prostate, ovary	Upregulated in cancers and linked to poor outcome	Small molecules inhibiting interaction with let-7	(Alajez et al., 2015; Reachy et al., 2012; Hamano et al., 2012; King et al., 2011; Madison et al., 2013; Molenaar et al., 2012; Nadinmity et al., 2012; Nguyen et al., 2014; Piskounova et al., 2011; Roos et al., 2016; Tu et al., 2015; Urbach et al., 2014; Viswanathan et al., 2009; L. Wang et al., 2018; Xiaojun Yang et al., 2010)