

AGO-RBP crosstalk on target mRNAs: Implications in miRNA-guided gene silencing and cancer

Pavan Kumar Kakumani

Department of Biochemistry, Memorial University of Newfoundland, 45 Arctic Avenue, St. John's, NL A1C 5S7, Canada

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ABSTRACT

MicroRNAs (miRNAs) and RNA-binding proteins (RBPs) are important regulators of mRNA translation and stability in eukaryotes. While miRNAs can only bind their target mRNAs in association with Argonaute proteins (AGOs), RBPs directly bind their targets either as single entities or in complex with other RBPs to control mRNA metabolism. miRNA binding in 3' untranslated regions (3' UTRs) of mRNAs facilitates an intricate network of interactions between miRNA-AGO and RBPs, thus determining the fate of overlapping targets. Here, we review the current knowledge on the interplay between miRNA-AGO and multiple RBPs in different cellular contexts, the rules underlying their synergism and antagonism on target mRNAs, as well as highlight the implications of these regulatory modules in cancer initiation and progression.

Introduction

MicroRNAs (miRNAs) are small non-coding RNAs that repress gene expression by base-pairing with complementary sites, typically found in 3' untranslated regions (3' UTRs) of target mRNAs [1]. miRNAs are predicted to target over 50% of all human protein-coding genes post-transcriptionally, enabling their regulatory roles in physiological and pathological processes [2]. Global dysregulation of miRNA expression is a discernible feature in cancer [3], and miRNAs can either promote or impede tumor development depending on the presence of their targets and the cellular context [4]. Alterations in miRNA-mediated gene regulation are implicated in key processes of tumorigenesis, such as apoptosis, angiogenesis, migration, and invasion [5].

MiRNAs are short double-stranded RNA molecules of 21-23 nucleotides (nt) in length. Long hairpin transcripts, called primary miRNAs (pri-miRNAs), are processed by the Drosha-DGCR8 complex in the nucleus yielding precursor miRNAs (pre-miRNAs). The pre-miRNAs are then processed by the Dicer complex in the cytoplasm, producing mature miRNAs [6]. Fully processed mature miRNAs consist of a guide strand and a passenger strand which are loaded onto Argonaute (AGO) proteins, the essential components of miRNA-induced silencing complexes (miRISCs). Among the four AGO proteins (AGO1-4) found in mammals, AGO2 is the most studied and has endonuclease activity. Briefly, mature miRNAs are loaded onto AGO, the passenger strand is released, and the guide strand directs the AGO complex to complementary sites on mRNAs. Once the miRNA-mRNA interaction is

initiated, AGO recruits TNRC6 and CCR4-NOT complexes, to facilitate translational repression and/or de-adenylation followed by degradation of targeted mRNAs [7]. However, multiple local and global determinants modulate target binding and silencing efficacy, including target abundance, number and accessibility of miRNA binding sites, and binding of RBPs on the 3' UTR of targets [8].

RBPs are essential players in mRNA metabolism which regulate splicing, transport, translation, and degradation [9]. Interestingly, about half of the RBPs identified thus far bind mRNAs and manifest their function by regulating the fate of target mRNAs. RBPs together with mRNAs form ribonucleoprotein complexes (mRNPs) and the composition of mRNPs is dynamic and depends on the specifics of mRNA metabolism. Altered expression, localization, and post-translational modification of RBPs contribute to tumorigenesis, by increasing the expression of oncogenes or decreasing the expression of tumor suppressor genes [10,11].

RBPs bind RNAs through RNA binding domains (RBDs) which include the K-homology domain (KH), RNA recognition motif (RRM), Zinc finger domain (ZNF), Pumilio homology domain (PUM), cold shock domain (CSD), double stranded RNA binding domain (dsRBD) and others [10]. They recognize common mRNA features such as the 3' poly (A) tail and the sequence motifs or secondary structures present in mRNA 3' UTRs [9]. The 3' UTRs of mammalian mRNAs can be as long as 10 kilobases and are bound by different miRNAs and RBPs [12]. Genome-wide analysis of mRNAs reveals that nearly half of the mammalian genes express isoforms varying in 3' UTR length as a result

E-mail address: pavan.kakumani@mun.ca.

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of alternative polyadenylation (APA) [13]. For several genes, mRNA isoforms with shorter 3' UTRs are expressed at higher levels in transformed cells than in non-transformed cells [14]. Variations in 3' UTR lengths determine the degree of association of RBPs and the miRISCs with potential consequences for tumorigenesis [10,15,16].

In this review, we will discuss various RBPs pertinent to their

Table 1
Examples of antagonistic interactions between miRNA-AGO and RBPs

RBP	miRNA	Type of Cancer/Cells	Target mRNA(s)	Effect	Refs.	
HuR	miR-16	Colorectal	COX-2	Promotion of tumorigenesis	[17]	
	miR-331-3p	Prostate	ERRB2	Resistance to therapy	[18]	
	miR-122	Multiple cancer lines	CAT-1	Control of cellular stress	[19]	
	miR-548c-3p	Cervical cancer cells	TOP2A	Control of cell cycle	[20]	
	miR-494	Cervical cancer cells	Nucleolin	Control of cell proliferation and survival	[21]	
	miR-200b	Macrophage	VEGF-A	Angiogenesis	[22]	
	miR-25-3p	Human 293 cells	BTG2, CDK16	ND	[23]	
	circAGO2	Gastric	EIF4EBP3, MAP4K1, SLC2A4	ND	[24]	
	Pumilio	miR-30, miR-25, miR-17	Human 293 cells	FNIP1, TOB1, VLDLR	ND	[25]
		miR-297, miR-299	Myeloid cells	VEGF-A	Hypoxia	[26]
hnRNPL	miR-297, miR-299	Leukemia	CEPBA	Promotion of oncogenic signalling	[27]	
hnRNPE2	miR-328	Leukemia	CEPBA	Promotion of oncogenic signalling	[27]	
hnRNPK	miR-149-3p, miR-193b-5p	Cervical cancer cells	PLK1	Inhibition of apoptosis	[28]	
IGF2BP1	miR-183	Colorectal	BTRC	Drug resistance	[29]	
	miR-340	Melanoma	MITF	Inhibition of apoptosis	[30]	
	Multiple miRNAs	Ovarian	SIRT1	Cell survival and invasion	[31]	
	Let-7	Ovarian	IGF2BP1, HMGA2, LIN28B	Promotion of tumor growth and metastasis	[32]	
IGF2BP2	Let-7	Glioblastoma	CCND1, PEG10, HMGA1/2, IGF2BP3	Promotion of tumor cell growth, self-renewal and migration	[33]	
	miR-195	Colorectal cancer	RAF-1	Preservation of cancer stem cells	[34]	
IGF2BP3	Let-7	Multiple	HMGA2	Promotion of cell proliferation and survival	[35]	
Rbm38	miR-150, miR-206	Breast cancer	c-Myb, Cx43, p21	Progression of tumors	[36]	
FMRP	miR-328	Neuronal cells	MAZ	Cellular stress and cell cycle control	[37]	
DND1	miR-221, miR-372	Germ cell tumors	p27, LATS-1	ND	[38]	
	miR-21	Squamous cell carcinoma	MSH2	suppression of tumorigenesis	[39]	
FAM120A	ND	Embryonic stem cells	Poly(G) rich	suppression of tumorigenesis	[40]	
CSDE1	miR-129-5p	Melanoma cells	PMEPA1	ND	[41]	

involvement in the function of miRNA-AGO complexes on specific target mRNAs and the outcome of gene silencing (Tables 1 and 2, Figs. 1 and 2) with a focus on recent advances and new insights into malignant transformation.

Interplay between miRNA-AGO and RBPs on target mRNAs

miRNAs control the translation and abundance of their target mRNAs even when there is no significant change in miRNA expression levels. Among the potential targets of a specific miRNA, only a subset of mRNAs are subjected to miRNA regulation. These phenomena imply regulatory mechanisms downstream of miRNA biogenesis that influences miRNA activity. An expanding number of studies report the interplay between miRNA-AGO and RBPs on target 3' UTRs in determining the outcome of miRNA-guided gene regulation.

HuR

Human antigen R (HuR) is a ubiquitously expressed protein that binds AU-rich element (ARE) containing transcripts and controls their stability [57]. Subcellular localization of HuR to the cytoplasm is critical for its role in mRNA metabolism [58]. HuR is overexpressed in numerous cancers, including ovarian, breast, lung, colorectal and pancreatic. Besides its enhanced expression, HuR regulates

Table 2
Examples of co-operative interaction between miRNA-AGO and RBPs

RBP	miRNA	Type of Cancer/Cells	Target mRNA(s)	Effect	Refs.
HuR	Let-7a	Cervical cancer cells	c-Myc	Promotion of tumorigenesis	[42]
	miR-26	Primary neurons	Rgs4	ND	[43]
Pumilio	miR-19a/b-3p, miR-130b-3p, miR-17	HEK293	MSMO1	ND	[23]
	miR-221/222	Glioblastoma	p27 ^{Kip1}	Cell cycle control	[44]
	miR-502, miR-125b	Bladder	E2F3	Inhibition of tumorigenesis	[45]
	miR-101	Prostate and Lung cancer cells	MCL1	Induction of apoptosis	[46]
hnRNPI	miR-101	Prostate and Lung cancer cells	MCL1	Induction of apoptosis	[46]
hnRNPD	Let-7	Cervical cancer cells and fibroblasts	PDP2, POLR2D	ND	[47, 48]
	miR-196a	Cervical cancer and Leukemia cells	HOXB8, IFI16	ND	[49]
TTP	miR-16	HEK293, S2	TNF, COX2	ND	[50]
IGF2BP3	miR-9, miR-128	Pancreatic cancer cells	ZFP36L1, DCBLD2, CLND1	Promotion of invasion	[51]
Rbm38	miR-203	Breast and colorectal cancer cells	p63	ND	[52]
FUS	miR-200c	HEK293	ZEB1	ND	[53]
CFIm25	miR-95 and miR-124	Hepatocellular carcinoma	CCT5, UBA5	Inhibition of cell proliferation	[54]
CPEB1/2	miR-580	Breast cancer	TWIST-1	Inhibition of EMT	[55]
SFPQ	Let-7	HEK293, RAW 264.7	LIN28A	ND	[56]

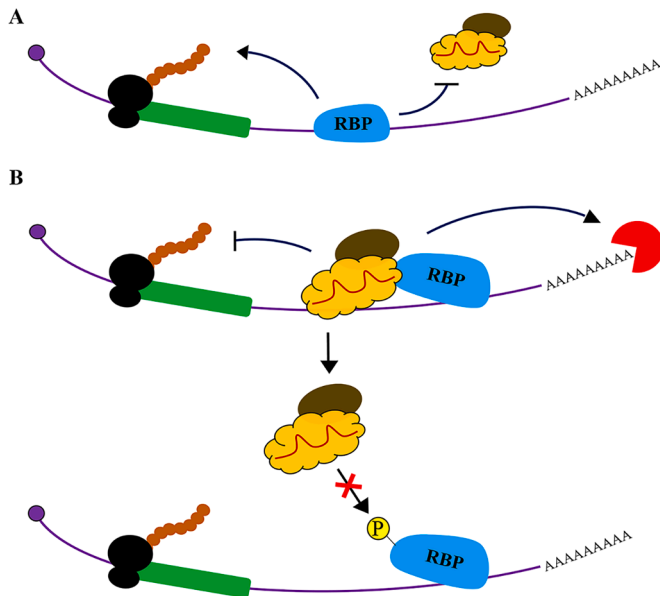


Fig. 1. Models of antagonistic miRNA-AGO: RBP interactions on target mRNAs. (A) The RBP competes with miRNA-AGO to bind the mRNA 3' UTR and antagonizes miRNA-guided target repression. (B) The interaction between an RBP and miRNA-AGO is disrupted by the phosphorylation of the RBP, therefore hindering the repression of miRNA-targeted mRNAs. RBPs are presented in Blue, AGO in Yellow, TNRC6 in Brown, Exonucleases in Red, and Ribosomes in Black while the Coding region of the mRNA in Green.

miRNA-targeted mRNAs involved in cell proliferation, metastasis, invasion, and angiogenesis [59]. For instance, in human liver cells, under stress, HuR binds the cationic amino acid transporter 1 (CAT1) mRNA and inhibits the recruitment of miR-122/AGO complex to target sites in the 3' UTR, thus relieving CAT1 mRNA repression [19]. Similarly, in colorectal cancer, HuR binds AREs in target mRNAs and hinders miR-16 guided repression of COX2 to promote tumorigenesis of intestinal tumors [17]. In prostate cancer, HuR binds U-rich elements in the 3' UTR of ERBB-2 and antagonizes miR-331-3p function [18]. Likewise, HuR enhances the translation of DNA topoisomerase 2-alpha (TOP2A) and Nucleolin by competing with miR-548c-3p and miR-494 in cervical cancer lines [20,21]. In macrophages, HuR and miR-200b compete to regulate the expression of Vascular Endothelial Growth Factor-A (VEGF-A) and angiogenesis [22]. Furthermore, HuR interaction with the intronic circular RNA, circAGO2 facilitates HuR binding to target 3' UTRs of EIF4EBP3, MAP4K1 and SLC2A4 mRNAs associated with gastric cancer progression [24]. In contrast, HuR binding of targets can also promote miRNA-AGO association in let-7-mediated repression of MYC in cervical cancer cells [42]. In neurons, HuR and miR-26/AGO2 synergistically act on Rgs4 mRNA, involved in the regulation of tumorigenic capacities [43]. Additionally, recent transcriptome wide analysis by Li et al., uncovered higher order regulatory modules of interaction between miRNA-AGO and HuR on specific mRNA 3' UTRs [23]. The study demonstrated that 10% of AGO2 binding sites overlap with 18% of HuR sites, suggesting AGO2 and HuR association has evolved to frequently co-occur towards a combinatorial regulation of mRNAs. Individual characterization of high-fidelity targets revealed that HuR antagonizes miRNA-guided repression of BTG2 and CDK16 but cooperates with miRNA-AGO on MSO1 3' UTR [23]. While BTG2 acts as a tumor suppressor [60], the roles of CDK16 and MSO1 need to be determined in terms of cancer development. Collectively, the interactions between HuR and miRNA-AGO on different mRNAs indicate that the overall contribution of these modules to mRNA control is substantial in malignant transformation.

Pumilio

Pumilio (PUM) proteins function as repressive factors through mRNA destabilization and translational inhibition. They contain PUF RNA-binding domains that recognize the motif, UGUANAUA, located primarily in the 3' UTR of target mRNAs [61]. Abnormal expression of PUM proteins (PUM1 and PUM2) is associated with several types of cancers such as bladder, breast and ovarian [62]. The effects of PUM proteins on mRNA metabolism are case-specific and involve interaction with additional factors and changes in 3' UTR secondary structures upon PUM binding [63]. For instance, phosphorylation of PUM facilitates its binding to 3' UTR of p27^{Kip1} mRNA, which induces a local conformational rearrangement, making the miR-221/222 complementary sites accessible for AGO binding and thus enabling miRNA-induced repression of p27^{Kip1} [44]. Interestingly, p27^{Kip1} is a crucial cell cycle inhibitor and acts as a tumor suppressor in glioblastoma [64]. In addition, PUM shares co-operative interactions with AGO2 on E2F3 mRNA, an oncogene that regulates cell proliferation and apoptosis. PUM1 and PUM2 proteins downregulate E2F3 expression in association with miR-503 and miR-125b in bladder carcinoma [45]. Of note, several cancer cells escape PUM-mediated regulation by shortening the 3' UTR of E2F3 mRNA, eliminating PUF RNA-binding motifs and thus disabling PUM-mediated repression [25]. Recent transcriptomic studies uncovered that miRNA binding sites are enriched in the vicinity of PUM sites, and co-occurrence of PUM along with miRNA sites in stem loops or sites of low accessibility correlates with repression of the mRNA [25]. Furthermore, Sternburg et al., revealed an overall predominance of co-operative interactions between PUM and AGO2 in altering gene expression [25]. Individual validation for a subset of targets confirmed an antagonistic co-regulation of FNIP1, TOB1 and VLDLR, which shows that Pumilio, a normally repressive factor, can take on a stabilizing role in a context-dependent manner. Interestingly, VLDLR is abnormally expressed in multiple cancers, namely gallbladder, gastric and breast and has critical roles in tumor development [65–67]. TOB1 acts as a tumor suppressor in multiple cancers, and FNIP1 is a binding partner of FLCN, a tumor suppressor in kidney cancer [68]. Despite these relationships, whether AGO2-PUM interactions on these targets contribute to the pathogenesis of each type of cancer remains an open question.

hnRNPs

Heterogeneous nuclear ribonucleoproteins (hnRNPs) are sequence specific regulators of mRNA splicing but also control mRNA stabilization and translation [69]. The altered expression of hnRNPs in multiple cancer types suggest an association with tumorigenesis [70]. hnRNPs are predominantly present in the nucleus during steady state; however, their localization to cell cytoplasm alters the translational output of target mRNAs [69,70]. For instance, during hypoxia, hnRNPL translocates to the cytoplasm, competes with the miRNAs, miR-297 and miR-299 and binds to CA-rich elements (CAREs) in the 3' UTR of VEGF-A to hinder its repression [26]. Similarly, hnRNPE2 was shown to bind C-rich regions in the 5' UTR of CCAAT/enhancer binding protein- α (CEPBA) mRNA, a key regulator of myeloid differentiation. Here, the C-rich mature form of miR-328 competes with CEPBA for binding to hnRNPE2 in a RISC-independent manner [27]. Likewise, hnRNPK influences binding of PLK1 mRNA to AGO2 and competes for C-rich motifs on 3' UTR with miR-149-3p and miR-193b-5p, regulating PLK1 expression and associated apoptosis and drug resistance [28]. In contrast, hnRNPI enhances miR-101-guided AGO2 interaction with MCL1 mRNA, thereby regulating miR-101-induced apoptosis and cell survival [46]. Apart from hnRNP interactions with either the miRNA or the target mRNA, hnRNPD facilitates the binding of let-7b to AGO2 and therefore enhance let-7b/AGO2 interaction with target mRNAs towards let-7b mediated repression of PDP2 and POLR2D [47,48]. In addition, Wu et al. reported that hnRNPD and AGO2 binding is co-operative for HOXB8 and IFI16 mRNAs [49]. Therefore, it is likely that direct

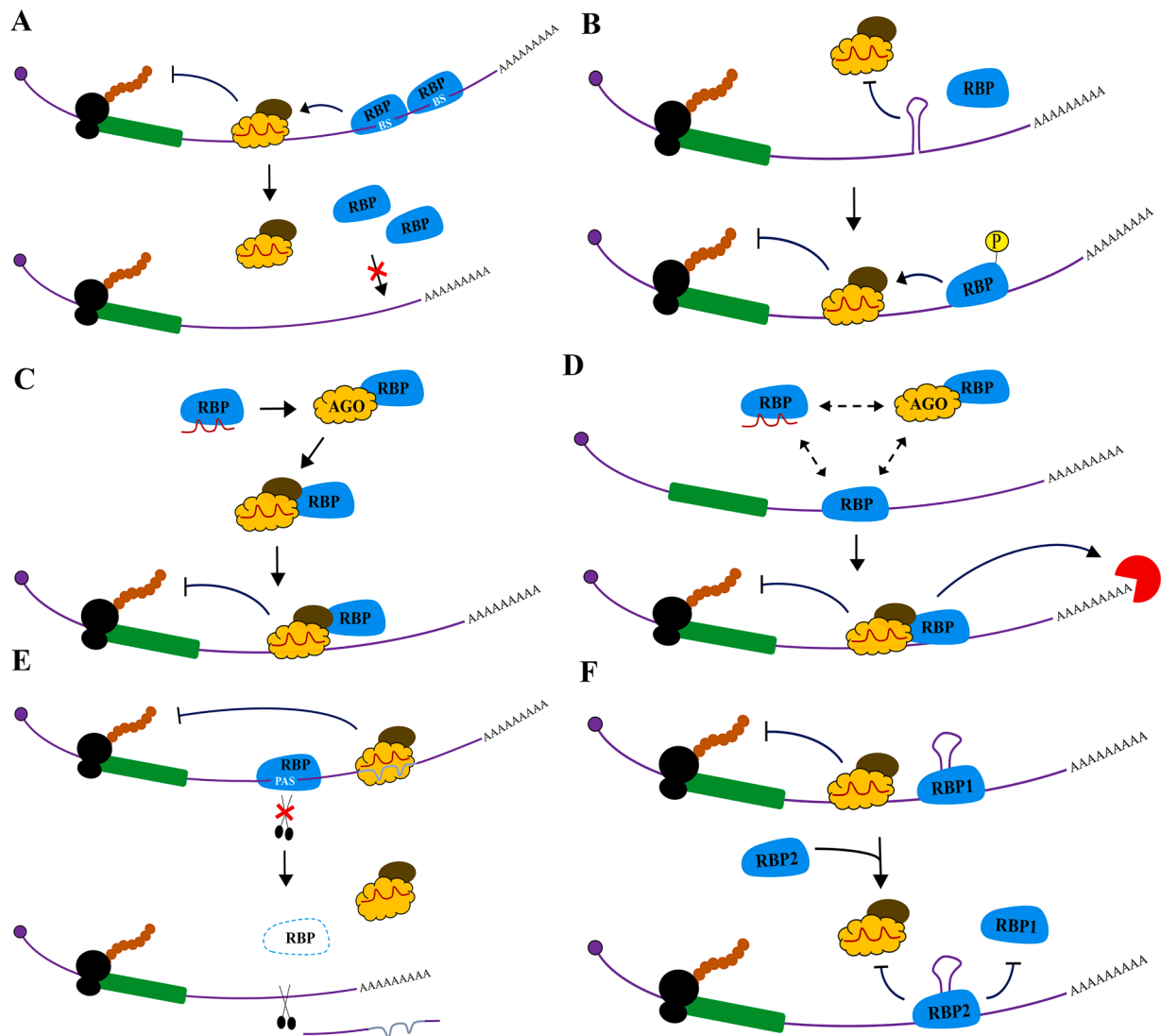


Fig. 2. Models of co-operative miRNA-AGO: RBP interactions on target mRNAs. (A) The RBP binds multiple sites on the target mRNA and facilitates the interaction between miRNA-AGO and complementary miRNA sequences in the 3' UTR, thereby cooperating in gene silencing. However, shortening of 3' UTR results in the loss of RBP binding sites (BS), thus affecting miRNA-AGO association with the target mRNA and its regulation. (B) Structures in the 3' UTR impede the binding of miRNA-AGO to target sites. Phosphorylated RBPs resolve these secondary structures, thereby allowing the binding of miRNA-AGO to miRNA complementary sites in mRNA 3' UTRs towards their repression. (C) The RBP assists in the loading of miRNAs into AGO and promotes miRNA-AGO binding to target sites in 3' UTR for gene silencing. (D) The RBP can simultaneously bind both miRNA and its targets, and its interaction with AGO facilitates the formation of miRISC on respective mRNA 3' UTRs, thus enabling miRNA-guided decay of targets. (E) The RBP protects Poly(A) Signals (PAS) from cleavage, and loss of its expression leads to deletion of complementary sites for miRNA-AGO binding to the mRNA, resulting in loss of miRNA function. (F) Different RBPs (RBP1 and RBP2) have varied binding affinities towards secondary structures in the 3' UTR of mRNAs. Depending on their nature of interaction with AGO, they either facilitate the binding of miRNA-AGO to the miRNA complementary sites, leading to target repression or form a stable complex surrounding the secondary structures in 3' UTR of target mRNAs. Such an arrangement limits the access of miRNA-AGO complex to the target sites embedded in the secondary structures, thus negatively affecting gene silencing. RBPs are presented in Blue, AGO in Yellow, TNRC6 in Brown, Exonucleases in Red, and Ribosomes in Black while the Coding region of the mRNA in Green.

hnRNPD-AGO2 association facilitates their co-binding to the mRNA. Alternatively, hnRNPD binding to HOXB8 mRNA may expose the miR-196a binding site, much like Pumilio that exposes miR-221/222 sites in p27 mRNA by altering local RNA structures [44,49]. Altogether, these studies show that hnRNP proteins, through their expression in specific contexts and interactions with miRNA-AGO, alter the metabolic outcomes of target mRNAs in tumors.

Tristetraprolin

Tristetraprolin (TTP) is an ARE-binding protein that mediates mRNA decay and translational repression by interacting with their 3' UTRs [71]. TTP targets Tumor necrosis factor (TNF), cyclooxygenase 2

(COX2), and MYC, thereby regulating apoptosis and proliferation [72, 73]. TTP is downregulated in several tumors such as glioma, colon, gastric and liver cancers, and low TTP mRNA levels correlate with poor prognosis [74]. Several studies reported interactions between TTP, miRISC components, and the mRNA degradation machinery [75]. For example, TTP can induce mRNA decay by decapping, which requires binding to an ARE in the 3' UTR and interaction with the decapping complex. Additionally, TTP interaction with AGO2 enables miR-16-mediated repression of TNF and COX2 in human cells [50]. Besides, TTP dissociation from AGO2 increases ARE-mRNA stabilization [76]. These data suggest multiple and yet poorly understood mechanisms, where TTP and miRNAs promote mRNA degradation with implications in pathological phenomena.

IGF2BPs

The oncofetal IGF2 mRNA binding proteins (IGF2BPs) control mRNA transport, translation, and turnover during development and in cancer [77]. IGF2BP isoforms 1 and 3 enhance the viability, migration, invasion, and metastatic potential of tumors *in vitro* and *in vivo* [31,51]. IGF2BP1 controls the degradation of BTRC mRNA, which encodes the ubiquitin ligase β TrCP1, by disrupting the association of miR-183 and AGO2 with a target site in the BTRC coding region [29]. IGF2BP1 also targets the 3' UTR of a microphthalmia-induced transcription factor (MITF) isoform that is predominantly expressed in melanoma and prevents miR-340-mediated repression [30]. In addition, IGF2BP1 recruits mRNAs encoding IGF2BP1, HMGA2 and LIN28B into mRNPs devoid of let-7/AGO2, thereby protecting them from miRNA-guided silencing. It also interferes with miRNA-mediated decay of SIRT1 mRNA in ovarian cancer cells to promote tumor cell growth, self-renewal, and migration [31,32]. Likewise, in glioblastoma, IGF2BP2 interacts with AGO2 in an RNA-dependent fashion and binds to let-7 target sites. Such activity impairs miRNA-guided repression of targets, namely CCND1, PEG10, HMGA1/2 and IGF2BP3; responsible for glioblastoma stem cell maintenance [33]. In addition, IGF2BP2 promotes cell proliferation and survival in colorectal cancer by interfering with miR-195 driven RAF-1 degradation [34]. Similarly, IGF2BP3 protects and upregulates HMGA2 expression by opposing the interaction between let-7/AGO2 and HMGA2 mRNA [35]. In contrast, IGF2BP3 promotes the association of AGO2 with invasion-associated transcripts, namely ZFP36L1, DCBLD2, and CLDN1 in pancreatic ductal adenocarcinoma [51]. Furthermore, Muller S *et al.*, 2018 discovered that IGF2BP binding sites are enriched ~40 nucleotides upstream of miRNA target sites which overlap with AGO2-binding, suggesting broader regulation [31]. Collectively, these reports demonstrate that all three IGF2BPs promote tumorigenesis by modulating the miRNA-AGO directed degradation of oncogene-encoding mRNAs in cancer cells.

Rbm38

The RNA-binding protein Rbm38 is a target of the p53 family. Rbm38 regulates gene expression underlying several cellular processes, including cell growth and differentiation [78]. Rbm38 regulates the stability of its targets depending on the nucleotide composition of binding sites. For instance, it reduces p63 α/β mRNA levels by binding to AU/U- rich elements but enhances p63 γ mRNA levels by association with GU-rich elements [78,79]. In breast cancer, following DNA damage, p53 induces the expression of Rbm38 which in turn limits the accessibility of target sites of the miRNAs, miR-150 and miR-206 on 3' UTRs of c-MYB, CX43, and p21 mRNA to regulate cellular stress and cell cycle [36]. Further, Zhang Y *et al.*, 2019 showed that Rbm38 binds U-rich elements in the 3' UTR of p63 and recruits miRNA-AGO complex by interacting with AGO2. However, the Ser-195 phosphorylation of Rbm38 abrogates its association with AGO2, thereby hindering the binding of miR-203/AGO2 complex to p63 α mRNA for degradation. [52]. Of note, p63 over-expression is associated with malignant conditions, such as squamous carcinomas of the head, neck, and skin [80,81]. Since tumors with mutated p53 exhibit changes in Rbm38 expression, it is likely that the controlling action of Rbm38 over miRNA-AGO function on target mRNAs contributes to p53 activity in tumor progression.

FUS

FUS is a DNA/RNA-binding protein with a conserved RNA recognition motif (RRM) [82]. FUS is involved in multiple cellular processes, including transcription, pre-mRNA splicing, and APA [83]. FUS expression is inversely correlated with prostate tumor grade, and patients with high levels of FUS have longer survival rates and are less likely to have bone metastases [84]. Recently, Zhang T *et al.*, 2018 showed that FUS interacts with AGO2 in an RNA-dependent manner

[53]. FUS binds to miR-200c and is required for the optimal association between miR-200c and AGO2. The impairment of FUS's interaction with the 3' UTR of target mRNA ZEB1 is sufficient to reduce miRNA silencing. Interestingly, ZEB1 expression is associated with many aggressive tumors, including breast, lung, colorectal, liver and glioblastoma [85,86]. ZEB1 plays a crucial role in tumor dissemination, metastasis, and therapy resistance [87]. These reports add to the growing number of studies demonstrating the involvement of RBPs in a three-way interaction with AGO, miRNA and the mRNA [88].

FMRP

The Fragile X Mental Retardation Protein (FMRP) is an RNA binding protein that binds ~4% of mRNAs in the brain and affects their translation [89]. FMRP binds its target mRNAs in the coding region as well as in the 3' UTR, depending on cellular identity [90]. FMRP contains two RNA binding domains, protein binding K-homology domains KH1 and KH2 [91], as well as an arginine-glycine-glycine (RGG) box that binds G-Quadruplex RNA structures (rG4s) *in vitro* [92]. FMRP exhibits a bifunctional role in translational regulation of bound mRNAs through its interaction with the RNA helicase MOV10 [93]. Both FMRP and MOV10 directly interact with AGO and rG4s in mRNA 3' UTRs. MOV10 binding to FMRP increases the ability of FMRP to bind rG4s *in vitro*, forming a stable FMRP-MOV10 complex. This co-operation between FMRP and MOV10 inhibits AGO binding to miR-328 target sites embedded in rG4 on Myc-associated zinc finger protein (MAZ) mRNA, preventing its translational repression [37]. MAZ is abnormally expressed in multiple tumors including breast, prostate, and liver. It promotes cancer cell proliferation, migration, and invasion [94,95]. However, considering the ambiguity over the occurrence of rGs in the *in vivo* context of mRNAs, it is yet to be determined how FMRP interaction with MOV10 pertinent to rG4 resolution and the miRNA-AGO function contributes to cancer development.

DND1

Dead end 1 (DND1) is expressed in germ cells and binds uridine-rich regions (URRs) in the 3' UTRs of germline-specific genes. DND1 either sequesters mRNAs or physically displaces miRISC to alleviate miRNA-mediated suppression [38]. DND1 alleviates miR-372-mediated repression of large tumor suppressor 2 (LATS2) and miR-221 and miR-222-mediated repression of p27 by competing with these miRNAs to bind their targets in germ cell tumors [38]. Similarly, in squamous cell carcinoma, DND1 impairs miR-21 action on its target MSH2, thus suppressing tumorigenesis in skin [96]. In contrast, DND1 recruits the CCR4-NOT deadenylase complex to destabilize and repress RNAs associated with apoptosis and inflammation [39,97]. Together, these studies indicate that DND1 forms a network of post-transcriptional regulation for the maintenance of stemness and these mechanisms could be relevant in tumors with acquired multipotency.

FAM120A

FAM120A is a putative RBP and a component of Pur α -containing mRNP complexes through direct binding of IGF-II mRNA [98]. It acts as a scaffold for activation of several intracellular kinases, including Src, FAK, and PI3K, in response to oxidative stress, and IL13 receptor α 2 signalling in cancer cells [99,100]. Recently, FAM120A was shown to interact with AGO2 in mESCs. FAM120A binds homopolymeric tracts in 3' UTRs of mRNAs with poly(G) sequences, and its targets overlap with more than one third of mRNAs bound by AGO2 [40]. Further, FAM120A-bound targets are less sensitive to AGO2-mediated target degradation, suggesting FAM120A attenuates AGO2-mediated gene silencing. While the specific mechanism by which FAM120A binding counteracts miRNA-guided mRNA degradation is unclear, it is likely independent of miRNA-AGO2 binding to its targets, as the binding sites

of FAM120A and AGO2 do not directly overlap. Also, in light of FAM120A association with other RBPs, including IGF2BP1, IGF2BP3 and HuR, which cooperate and compete with miRNA-AGO to bind target mRNAs, it is possible that the regulatory effects of FAM120A can only be observed in a combinatorial module with the other regulatory RBPs.

CSDE1

Cold Shock Domain containing protein E1 (CSDE1), also known as UNR (upstream of N-Ras), is a member of the evolutionarily conserved CSD containing protein family [101]. CSDE1 plays an important role in a wide range of biological processes such as cell cycle, apoptosis, and differentiation [102,103]. CSDE1 acts as an oncogene in melanoma, glioma, colorectal and breast cancers while performing tumor suppressor functions in pheochromocytoma, paraganglioma, oral squamous cell carcinoma and in keratinocytes [104,105]. Recently, we reported that CSDE1 interacts with AGO2 within miRISC and particularly, in melanoma cells, this association is facilitated by target mRNAs [41,106]. CSDE1 and AGO2 share a total of 93 targets, including Prostate Transmembrane Protein, Androgen Induced 1 (PMEPA1), a protein that enhances tumorigenic properties in breast, lung cancers and glioblastoma whilst displaying anti-tumoral roles in prostate cancer [107–109]. CSDE1 competes with miR-129-5p/AGO2 to bind PMEPA1 mRNA and promote its expression at protein levels. Further, the loss of CSDE1 N-terminal cold shock domain (CSD1), which is required for CSDE1 RNA-binding, enhances AGO2 association with PMEPA1 mRNA leading to its repression [41]. This suggests that target recognition and occupancy by CSDE1 determines the degree of recruitment of miRNA-AGO2 complex to specific mRNAs involved in the development of tumorigenic phenotypes.

NUDT21/CFIm25

CFIm25 is a subunit of the heterodimer CFIm, a major factor that governs APA [110]. CFIm25 is necessary and sufficient to bind sequences specific for the poly(A)-site upstream component UGUA [111]. CFIm25 can function as a tumor suppressor and an oncogene in glioblastoma and chronic myelocytic leukemia, respectively [110,112]. CFIm25 interacts with AGO2 and co-localizes to discrete cytoplasmic loci called P-bodies in liver tumors [113]. Functional studies showed that CFIm25 promoted APA at distal sites, resulting in elongated mRNA 3' UTRs, which enhanced AGO2 binding to the targets of miR-95 and miR-124, notably CCT5 and UBA5 [54]. In addition, the loss of CFIm25 shortened the 3' UTRs of oncogenes in Hepatocellular Carcinoma (HCC) cells. The shorter 3' UTRs contained fewer miRNA binding sites, enabling the oncogenes to evade miRNA regulation, and become over-expressed in HCC, leading to unregulated cancer cell proliferation.

CPEB

The Cytoplasmic Polyadenylation Element Binding protein (CPEB) family includes 4 members (CPEB1-4), which regulate translation of their target mRNAs by binding to Cytoplasmic Polyadenylation Elements (CPE) in the 3' UTR [114]. CPEB proteins can repress or activate translation of target mRNAs by shortening or elongating the poly-A tail. CPEB1 acts as a tumor suppressor in mammary epithelial cells and controls Epithelial-to-Mesenchymal Transition (EMT) and metastatic phenotypes [115]. Similarly, CPEB2 acts as a tumor-suppressor by binding to Hypoxia Inducible Factor 1 Subunit Alpha (HIF1 α) mRNA and suppressing its translation under normoxic conditions but releasing it to allow translation under hypoxic conditions [116]. HIF1 α , under hypoxic conditions, stimulates genes promoting angiogenesis, migration, metastasis, and therapeutic resistance [117]. Twist-related protein 1 (TWIST1) is a known HIF1 α target and is highly relevant in EMT and metastasis formation in head and neck squamous cell carcinoma and non-small cell lung cancer [55,117]. Nairismagi ML *et al.*, 2012

identified miR-580, CPEB1 and CPEB2 as negative regulators of TWIST1 in an *in vitro* model of breast cancer and demonstrated co-operative effects between the CPEB and miR-580 sites [55]. Also, CPEB2 is unable to bind the shorter form of TWIST1 mRNA, preferentially expressed in metastatic cells which correlates with high TWIST1 expression, indicating CPEB-miR-580 axis regulates TWIST1 during tumor pathogenesis. These findings add to the growing number of studies demonstrating that cancer cells use 3' UTR shortening as a strategy to control the interplay between the miRNA-AGO and RBPs on mRNAs with oncogenic or tumor suppressor functions.

SFPQ

Splicing factor proline- and glutamine-rich protein (SFPQ) is a ubiquitous and abundant nuclear RBP involved in splicing, RNA transport, and apoptosis [118–120]. SFPQ is involved in multiple cancer types, including renal cell carcinoma, colorectal, liver, lung, and breast cancers [121]. Recently, Bottini S *et al.*, 2017. showed that SFPQ interacts with AGO2 in an RNA-dependent manner [56]. SFPQ associates to nucleoplasmic AGO2/miRISC through its interacting partners, Paraspeckle component 1 (PSPC1) and Non-POU domain-containing octamer-binding protein (NONO). SFPQ preferentially binds long 3' UTRs that harbour multiple copies of SFPQ-binding motifs, CUGU and UGUA and regulate the accessibility of miRNA-target sites. Here, SFPQ forms long aggregates on target 3' UTRs in the nucleus to modulate their folding for proper positioning/recruitment of miRNA-AGOs to select binding sites, namely on LIN28A 3'UTR. These results highlight the importance of nuclear miRNA targeting and the sequence features of mRNA 3' UTRs for subcellular allocation of post-transcriptional miRNA regulation. However, it is yet to be determined how PSPC1, NONO are involved in these mechanisms and the overall contribution of SFPQ-PSPC1-NONO complex to nuclear miRNA-AGO function in tumor pathogenesis.

Summary

miRNA function is often deregulated in cancer, and these variations are rarely caused by miRNA gene amplification or disruption. RBPs and their interacting partners mostly determine the changes observed in miRNA activity associated with tumorigenesis. The fact that 3' UTRs of mRNAs frequently contain multiple evolutionary conserved binding sites for both miRNAs and RBPs suggests that the interplay between RBPs and miRNAs is a crucial component of gene regulation. Although the list of miRNA-AGO: RBP interactions presented here keeps growing (Table 1–2), our comprehension of this functional relationship is relatively recent and still in its nascent stage.

Studies thus far provided us a glimpse of intricate associations between miRNA-AGO and RBPs on target mRNAs. However, it is yet to be determined, what's the net effect of miRNA-AGO: RBP interactions in the development of tumors and whether miRNA-AGO: RBP pairs are specific to the cancer type or share a pattern of target repression between different cancers and their cellular phenotypes. Since the earlier studies strongly suggest that the effects of interaction are dependent on the nature of target mRNAs, whether oncogenic or tumor suppressor, it would be intriguing for further studies to focus on the repertoire of target mRNAs bound by the miRISC in the absence or the over expression of each RBP and evaluate how the changes in mRNA binding by both miRNA-AGO and RBP manifest into tumorigenic capacities of cancer cells *in vivo*.

Challenges

For the past few years, considerable advances have been made in dissecting miRNA-AGO: RBP interactions underlying the tumorigenic properties of different cancers. However, there remain challenges in defining the contribution of these associations to the development of

tumors. For example, an RBP can have context dependent opposing effects on miRNA-AGO function in the repression of specific mRNAs. Also, a single miRNA can target multiple mRNAs, and RBP association with a particular miRISC varies depending on the extent of its binding to the repertoire of target mRNAs with oncogenic and/or tumor suppressor functions. Therefore, to determine the accuracy/mode of influence exerted by an RBP on miRNA-AGO function, at first, we need to know the number of miRNA binding sites along with their position relative to RBP binding and the contribution of each site to the silencing of target mRNAs under endogenous conditions. To acquire such information, we could make use of improved high throughput techniques such as iCLiP, which produces miRNA-target chimeras. These hybrid sequences will help identify and confer specificity to miRNA-target interactions *in vivo* and establish the link between a given miRNA and its target mRNA [122]. Additionally, another daunting task now faced by the scientific community studying AGO-RBP contribution to cancer is the comprehension of non-canonical interactions of AGO proteins in gene regulation. For instance, in quiescent cells, AGO2 promotes translation of specific ARE mRNAs in association with Fragile-X-Mental-Retardation syndrome Related protein 1a (FXR1a), p97 and PARN [123,124]. In Pancreatic Ductal Adenocarcinoma (PDAC) cells, AGO2 interacts with oncogenic KRAS, which affects the unwinding of miRNA duplexes and thus the binding of mature miRNA-AGO complex to target mRNAs in order to promote KRAS-mediated oncogenesis [125,126]. These complex layers of bi-directional regulation associated with AGO-RBPs often make it impossible to neatly classify their involvement in the control of gene expression into oncogenic or tumor-suppressive.

Outlook

Despite the challenges surrounding the context dependent function of miRNA-AGO and RBPs, studies over the last few years measuring RNA-RNA and RNA-protein interactions, as well as mRNA secondary structures, enabled us to connect networks of post-transcriptional regulation involving miRNAs, RBPs and decipher their relevance for cancer initiation and progression [9,10,122] (Figs. 1–2). And yet, the data generated so far is mostly from cell lines such as HEK or HeLa, of which may not reflect the real time scenarios that occur during the stages of malignant transformation *in vivo*. Thus, we need to revisit the already known -as well as explore new AGO-RBP interactions on specific mRNAs using transcriptome wide approaches in primary tumor cells along the stages of cancer progression to have a comprehensive understanding of their regulation. Alternatively, we could make use of animal cancer models that are physiologically relevant to gain the insights into AGO-RBP interactions on miRNA-targeted mRNAs with pathological consequences. Furthermore, in light of studies emerging to support the notion that multiple RBPs coordinately act on the miRNA-AGO complex, we could explore RBP-RBP interactions and their individual and cumulative binding patterns to define their combinatorial effects over miRNA-AGO recognition of targets towards gene silencing. We believe that a thorough knowledge of the interplay among RBPs, miRNAs and other mRNA-interacting molecules is paramount to understanding the complexity of post-transcriptional gene control surrounding aberrant mRNA metabolism in cancers. This exciting playground of RBPs and miRNA-AGOs still holds secrets that, when uncovered, will reveal networks with potential therapeutic benefits.

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CRediT authorship contribution statement

Pavan Kumar Kakumani: Conceptualization, Investigation, Visualization, Methodology, Data curation, Formal analysis, Validation,

Resources, Supervision, Funding acquisition, Project administration, Writing – original draft.

Conflict of Interest

The author(s) declare that no conflict of interests exists.

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Supplementary materials

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