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microRNAs and RNA-binding proteins

A complex network of interactions and reciprocal regulations in cancer

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In the last decade, an ever-growing number of connections between microRNAs (miRNAs) and RNA-binding proteins (RBPs) have uncovered a new level of complexity of gene expression regulation in cancer. In this review, we examine several aspects of the functional interactions between miRNAs and RBPs in cancer models. We will provide examples of reciprocal regulation: miRNAs regulating the expression of RBPs, or the converse, where an RNA-binding protein specifically regulates the expression of a specific miRNA, or when an RBP can exert a widespread effect on miRNAs via the modulation of a key protein for miRNA production or function. Moreover, we will focus on the ever-growing number of functional interactions that have been discovered in the last few years: RBPs that were shown to cooperate with microRNAs in the downregulation of shared target mRNAs or, on the contrary, that inhibit microRNA action, thus resulting in a protection of the specific target mRNAs. We surely need to obtain a deeper comprehension of such intricate networks to have a chance of understanding and, thus, fighting cancer.

Introduction

Our knowledge of the complexity of gene expression regulation in eukaryotes has been continuously expanding in the last decades, especially since when the modulation acting at the post-transcriptional level has been discovered and studied in its multiple aspects. Two great classes of regulatory molecules working post-transcriptionally are microRNAs (miRNAs) and RNA-binding proteins (RBPs). The former are tiny (20–23 nt) RNA molecules that bind to their specific target mRNAs by recognizing short sequences usually located in 3'UTRs, thereby determining a downregulation of the encoded protein, via either translation inhibition or mRNA degradation (for a comprehensive review, see refs. 1–2). Their synthesis starts in the nucleus where they are transcribed, mostly by RNA Polymerase II as long precursors called pri-miRNAs, then processed by the RNase III enzyme Drosha to yield ~70 nt hairpin precursors, pre-miRNAs.[3] Pre-miRNAs are exported to the cytoplasm where ~22 mer dsRNAs are excised by another RNase III enzyme, Dicer.[3] To produce the mature miRNA, one strand of the dsRNAs is inserted into the RNA-induced silencing complex (RISC), where the miRNA plays its role of negative regulator of mRNA stability or translation.[4]

RBPs too play their roles by binding to mRNAs, even if their binding sites are more widespread, spanning from the 5'UTRs to 3'UTRs through coding sequences, and their regulatory actions may be positive (activators) or negative (repressors), depending on the protein, the mRNA and the biological context.[5] The great interest dedicated by the scientific community to post-transcriptional mechanisms mediated by RBPs and miRNAs is confirmed by the recent development of several specific web tools, such as the comprehensive PTRguide (www.ptrguide.org/doku.php),[6] a continuously updated list of databases and tools for post-transcriptional regulation of gene expression (PTR) analysis, and doRiNA (dorina.mdc-berlin.de/rbp_browser/dorina.html),[7] focusing on the search for miRNAs and RBPs co-regulating mRNAs. Moreover, the results of CLIP-Seq approaches aimed at revealing direct interactions between RBPs and RNAs are recorded and updated in the StarBase database (http://starbase.sysu.edu.cn/index.php),[8] allowing the researcher to look up experimentally demonstrated interactions of specific RBPs to RNA regions in defined cell types and conditions.

Due to the great potential of fine-tuning gene expression characterizing both miRNAs and RBPs, their role has been widely investigated in virtually all biological fields, from physiology to pathology and, obviously, cancer. The role of miRNAs as key regulators in cancer has been extensively studied and understood, to such an extent that several miRNAs are nowadays classified as "oncomiRs" or, conversely, as tumor suppressor miRNAs.[9] As for miRNAs, the involvement of some RBPs in oncogenesis and tumor progression has been shown in several types of cancer.[10] Given the shared way of interaction with the target molecules and the established role of both kinds of molecules in cancer, it is easy to predict that they may interact on the same mRNA to achieve a highly refined modulation of the expression of the protein product.

This review focuses on diverse ways of functional interactions between miRNAs and RBPs in tumor models, describing reciprocal modes of direct regulation, where miRNAs regulate RBPs or vice versa, or where miRNAs and RBPs either cooperate or

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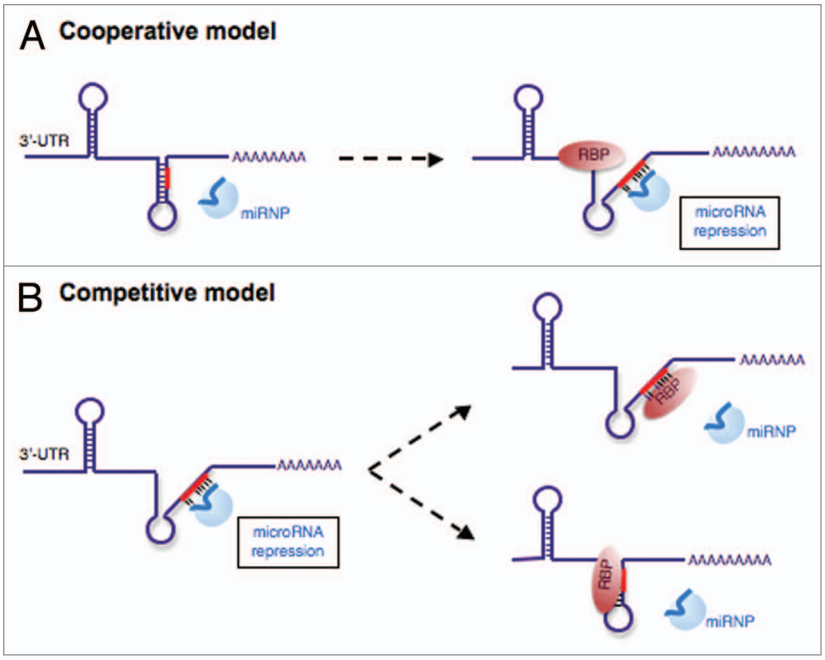

Figure 1. Ribonucleosome model depicting miR/RBP interplay in the regulation of the same target mRNA. (**A**) Cooperative model: RBPs can enhance the effect of miRNAs on shared target mRNAs and function as guides that mediate the opening of the structure, thereby allowing interaction between miRNAs and their low-accessibility targets. (**B**) Competitive model: RBPs can counteract miRNA regulation of target mRNAs by recognizing binding sites that overlap or are very close to the sequence bound by the "seed" region of the miRNAs hampered. On the contrary, in the context of non-overlapping sites, competition could occur by steric hindrance or by non-steric hindrance involving changes in the secondary structure of the mRNA.

counteract in the regulation of a specific mRNA (**Fig. 1**). We will also describe broader mechanisms of RNA-binding proteins affecting the general miRNA processing machinery or mRNA 3'UTR length, in turn yielding consequences on miRNA binding potential along the 3'UTR.

RNA-binding proteins that enhance miRNA function (Fig. 1A). It's easy to predict that a specific class of RBPs, those that take active parts in miRNA biogenesis, in fact result to behave as general enhancers of microRNA functions. Consequently, the dysregulation of such proteins is often observed in different types of human tumor cells. Recent examples regard Dicer1 overexpression in acute myeloid leukemia cells,[11] the widespread downregulation of several miRNA biogenesis components in hepatocellular carcinoma,[12] the observation that Dicer downregulation can be used to predict poor prognosis in chronic lymphocitic leukemia[13] and many others (as an example, see the extensive review about the prognostic significance of Dicer expression in human cancers[14]).

With reference to other RBPs, not directly involved in microRNA biogenesis, evidence collected over the past years have revealed that in human malignancies, key drivers of cell proliferation can be controlled by the cooperative effects of RBPs and miRNAs, where RBPs can enhance the effects of miRNAs, possibly via binding facilitation (**Table 1A and B**). In this regard, the Pumilio RBPs PUM1 and PUM2 were shown to cooperate with several miRNAs and function as guides that mediate the opening of the structure, thereby allowing interaction between miRNAs and their low-accessibility targets.[15-17] A comparative study of mRNAs interacting with Pumilio proteins showed a considerable enrichment of Pumilio-binding sites in the vicinity of predicted miRNA recognition sequences in human mRNAs, suggesting a widespread interaction of human Pumilio proteins with miRNA regulatory systems.[15] Kedde and collaborators[16] have demonstrated, in the MCF7 breast cancer cell line, that Pumilio promotes the regulatory effects of miR-221/222 on the $p27^{Kip1}$ mRNA by inducing a conformational change in the 3'UTR sequence of the $p27^{Kip1}$ mRNA and exposing the target sequences to miR-221/222. These interactions are significant, given that $p27^{Kip1}$ downregulation by miR-221/222 is essential for cell proliferation and may also have a central role in the development of cancer.[18,19] In another paper, Pumilio was shown to cooperate with some miRNAs to repress E2F3, an oncogene with strong proliferative potential, often dysregulated in bladder cancer.[17] Interestingly, the authors found that bladder carcinoma cell lines selectively downregulate miRNAs that cooperate with Pumilio to target E2F3, and that the 3' end of E2F3 mRNA is commonly shortened in multiple tumor cell lines, thus removing the Pumilio regulatory elements. These findings led them to speculate that in tumors where a key driver of cell proliferation ($p27^{Kip1}$ or E2F3) is controlled by the cooperative effects of Pumilio and miRNAs, manipulating Pumilio activity may provide a novel opportunity to re-establish/strengthen the regulatory potential of miRNAs and suppress tumor cell proliferation.

A similar conclusion was drawn for the case of the oncogene TWIST whose 3' UTR is shortened during cancer progression. Nairismägi and collaborators[20] identified miR-580, CPEB1 and CPEB2 as negative regulators of TWIST1 in an in vitro model of breast cancer progression, and demonstrated cooperative effects between the CPEB and miR-580 sites. In addition, they have shown that CPEB2 is not able to bind the shorter form of TWIST1 mRNA preferentially expressed in metastatic cell lines. This, in turn, correlates with high TWIST1 expression in those cells and indicates that the CPEB-miR-580 axis is important in regulating TWIST1 expression during oncogenesis.

RNA-binding proteins that contrast miRNA function (Fig. 1B). The activity of miRNAs, besides being enhanced, can also be hindered by RBPs bound to target 3'UTRs (**Table 1A and B**). Competition for binding sites has focused on Dnd1, an RNA-binding protein that mediates germ-cell viability and suppresses the formation of germ-cell tumors.[21] Dnd1 has been shown to interact with the 3'UTRs of mRNAs, such as $p27^{Kip1}$ and LATS2. Binding of DND1 to the 3'UTRs of these transcripts blocks the inhibitory function of miRNAs targeting these mRNAs, and in this way, DND1 helps to maintain $p27^{Kip1}$ and LATS2 protein

Table 1A. Examples of RBP-miRNA cooperation

RBP	miRNA	Type of cancer	mRNA target and effect	Reference
Pumilio	mi221/222	Breast cancer, glioblastoma	p27 induction of proliferation	16
Pumilio	miR-502, miR-125b	Bladder cancer	E2F3 tumorigenesis inhibition	17
CPEB1, CPEB2	miR-580	Breast cancer	TWIST-1, EMT inhibition	20
HuR	let-7a	Cervical cancer cell lines	c-MYC tumorigenesis promotion	10

Table 1B. Examples of RBP-miRNA competition

RBP	miRNA	Type of cancer	mRNA target and effect	Reference
DND1	miR-221 miR-372	Germ cells tumors	p27, LATS-1 suppression of tumorigenesis	21
DND1	miR-21	Squamous cell carcinoma	MSH2, suppression of tumorigenesis	22
RBM38	miR-150 miR-206	Breast cancer	c-MYB, CX43, p21; Cellular stress and cell cycle control	23
CRD-BP	miR-340	Melanoma	MITF, cancer cell survival and invasion	24
CRD-BP	miR-183	Colorectal cancer	β*TrCP*1, inhibition of apoptosis	25
HNRNP E2	miR-328	Blast crisis chronic myelogenous leukemia	CEBPA Impairment of leukemia blast survival, rescue of differentiation	26
HuR	miR-16	Colorectal cancer	COX-2, tumorigenesis promotion	66
HuR	miR-331	Prostate cancer	ERBB2, resistance to therapy	69
HuR	miR-122	Several cancer cell lines	CAT-1, cellular stress control	66
HuR	miR-548c	Cervical cancer cell lines	TOP2A, cell cycle control	70

expression in a germ-cell tumor cell line. Similarly, in squamous cell carcinoma, DND1 impairs miR-21 action on its target MSH2, thus suppressing tumorigenesis in skin.[22]

As for Dnd1, RBM38 function too was connected to miRNAs. Léveillé et al.[23] results portray a model whereby RBM38 potentially inhibits miRNA function on many mRNAs.[23] This occurs when RBM38 is induced in a p53-dependent manner following DNA damage. P53 modulates miRNA production and biogenesis at several levels, associating with essential components of the miRNA biogenesis machinery. The authors unravel an extra layer of miRNA regulation by p53 that relies on the modulation of the activity of specific miRNAs on p53 targets. They show that p53 induces the RNA-binding protein RBM38, which, in turn, limits the accessibility of miRNA sites on the 3'UTRs of its target gene transcripts. As functional impairment of the p53 pathway is instrumental for tumor progression, RBM38 could be important for full p53 function. The fact that a significant proportion of wt p53 tumors, like breast and prostate cancer, possess DNA methylation of RBM38 promoter region, suggests an active mechanism to silence RBM38 in those tumors.[23]

Another example of RBP/miRNA competition involves CRD-BP that has been shown to be important for the growth, survival and invasion of many types of cancer cells, through the regulation of different target mRNAs.[24,25] In melanoma cell lines, CRD-BP stabilizes and increases the oncogene MITF expression by counteracting the miR-340-mediated degradation of MITF mRNA.[20] This contrasting activity was shown also in colorectal cancer cells where CRD-BP interferes with miR-183 function, resulting in the stabilization of β*TrCP1* mRNA.[25] It's interesting to note that this is one of the few examples in which the interplay between the RNA-binding protein and the miR does not take place on the 3'UTR but within the coding region of the target mRNA.

All RBPs here reported to counteract miRNA regulation of target mRNAs, Dnd1, RBM38 and CRD-BP, recognize binding sites that overlap or are very close to the sequence bound by the "seed" region of the miRNAs hampered; this could suggest a mechanism of action in which, with overlapping binding sites, direct competition between the microRNA and the RBP is possible, whereas in the context of non-overlapping sites, competition could occur by steric hindrance or by non-steric hindrance

Table 2. Examples of RBP-miRNA reciprocal regulations

RBP	miRNA	Type of cancer	Mode of action	Reference
HuR	miR-519	cervical, colon and ovarian carcinoma cell lines	miR-519 downregulates HuR thus reducing proliferation	77
HuR	miR-519	cancer specimens of ovary, lung and kidney	inverse correlation of miR-519 and HuR protein in cancer and healthy specimens	78
HuR	miR-125a	breast cancer	miR-125a targets HuR, thus reducing proliferation and migration, while inducing apoptosis	80
CPEB2, CPEB3, CPEB4	miR-92 miR-26	neuroblastoma cell line	miR-92 and miR-26 target CPEBs	27
CPEB4	miR-550a	hepatocellular carcinoma	miR-550a targets CPEB4 thus inducing migration and invasion	32
DND1	miR-24	tongue squamous cell carcinoma	miR-24 targets DND1 thus reducing p27 expression, increasing proliferation and impairing apoptosis	34
Msi1	miR-34a, miR-101, miR-128, miR-137 miR-138	glioblastoma and medulloblastoma cell lines	miR-34a and the others target Msi1, thus reducing proliferation	35
Dicer	miR-103 miR-107	breast cancer	overall attenuation of miRNA biosynthesis; metastasis formation	45
Dicer	let-7	non-small-cell lung cancer cells	reduction of a large number of mature miRNAs	46
QKI	miR-20a	glioblastoma	QKI associates with and stabilizes mature miR-20a, thus contributing to the inhibition of TGFβ signaling	47
AUF1	General reduction of mature microRNA production	HeLa cell line; cancer tissue arrays of colon, stomach, breast, kidney, liver and pancreas	AUF1 binds to Dicer mRNA reducing its stability	51
RBM3	General reduction of mature microRNA production	neuroblastoma cell line	impairment of pre-miRNP access to Dicer complexes	54

involving changes in the secondary structure of the mRNA (**Fig. 1B**). Another possibility could be that RBPs change the subcellular localization of an mRNA, taking it out of reach of miRNAs.

An interesting case of miRNA/RNP interplay is that reported by Eiring et al.[26] They found that miR-328, a miRNA involved in differentiation rescue and survival impairment of leukemic blasts, not only functions through base paring with its own target (i.e., PIM1), but it is able to behave as an RNA decoy and to interfere with the activity of the translational inhibitor hnRNP E2. In fact, the mature form of miR-328 harbors a sequence element that resembles the hnRNP E2-binding site contained in the mRNA of CEBPA, a master regulator of myeloid differentiation. MiR-328 competes with CEBPA mRNA for binding to hnRNP E2: it interacts in a seed sequence-independent manner with the RBP and, in this way, prevents and displaces CEBPA mRNA binding for hnRNP, thus E2 rescuing CEBPA mRNA translation. Altogether, these data reveal the dual ability of a miRNA to control cell fate both through base pairing with mRNA targets and through a decoy activity that interferes with the function of regulatory proteins.

RNA-binding proteins that are regulated by miRNAs. The functional relationship between RBPs and miRNAs can be exerted also via the regulation of RBP expression by specific miRNAs (**Table 2**). This obviously results in a modulation of the effects played by RBPs and, consequently, in a modulation of the RBP-controlled genes. One might consider this mechanism as an additional way through which miRNAs can broadly affect gene expression and contribute to the great diversity characterizing cancer cells.

Among the first examples of such a regulatory connection are the mRNAs encoding for three paralogs of CPEB2 family, namely CPEB2, CPEB3 and CPEB4, strongly enriched in brain and involved in the post-transcriptional regulation of specific target mRNAs: the human CPEB2 mRNAs 3'UTRs span from a minimum of 3,570 nt to a maximum of 4,172 nt, in all cases greatly exceeding the respective CDS lengths. The CPEB2 mRNA members were shown to undergo common regulation by miR-92 and miR-26, in the neuroblastoma cell line SK-N-BE.[27] Of note, both miR-92 and miR-26 are deeply involved in cancer biology, miR-92 being encoded in two MYC-driven oncomiR clusters,[28,29] and mir-26 playing opposite roles in different types of cancers, i.e., tumor suppressor in nasopharyngeal carcinoma[30] or oncomiR in high-grade glioma.[31] Very recently, another miRNA, miR-550a, has been shown to target CPEB4 in human hepatocellular carcinoma (HCC),[32] where miR-550a induces in vitro migration and invasion. Moreover, those authors have found an inverse correlation between miR-550a and CPEB4 expression in HCC tumor specimens, and have described a positive association between CPEB4 expression and patients' survival. Thus, as the

CPEB2 family members are known key players in cancer development in vitro and in vivo,[30-33] the recent data about their regulation by miRNAs add an interesting degree of complexity to the pattern of expression modulation in cancer.

Another miRNA shown to play an "oncomiR" role through the specific regulation of an RNA-binding protein is miR-24 in tongue squamous cell carcinoma, the most frequent kind of oral carcinoma.[34] By using tumor specimens and cell lines, Liu et al. showed that miR-24 works via the specific downregulation of the RNA-binding protein dead end 1 (DND1),[35] in turn yielding a reduction in $p27^{Kip1}$ production, enhanced proliferation and reduced apoptosis. As discussed above, one of the ways to modulate $p27^{Kip1}$ expression at the post-transcriptional level is the interference between Dnd1 and miR-221/222 on $p27^{Kip1}$ 3'UTR.[16] We can thus envisage a regulatory axis involving at least three miRNAs (miR-24, miR-221 and miR-222) and one RNA-binding protein, Dnd1, all converging onto $p27^{Kip1}$ regulation in transformed cells.

A very interesting case is that of the RNA-binding protein Musashi 1 (Msi1), that acts at the translation level to control stem cell fate, nervous system development and tumorigenesis.[36] Vo et al.[37] recently showed that a class of tumor suppressor miRNAs (miR-34a, -101, -128, -137 and -138) regulate Msi1 in glioblastoma and medulloblastoma cells by cooperatively binding to its 3'UTR, thus negatively affecting proliferation of glioblastoma cells. A few months later, a further paper from the same group added a new piece to the intriguing regulatory network involving, and acting on, Msi1: the authors unveiled that another RBP, HuR, works on Msi1 mRNA increasing its stability and promoting its translation.[38] Moreover, they provided evidence that expression of HuR and Msi1 correlate positively in clinical glioblastoma samples, conferring strong clinical implications to their observation. It appears that the miRNA and the HuR binding sites along Msi1 3'UTR do not overlap, possibly suggesting that the two ways of regulation act independently on the very long Msi1 3'UTR.

A further example worth including in this list of miRNAs regulating RBPs is miR-503, shown to downregulate CUGBP1 mostly by binding to sites located in CUGBP1 coding region, and then recruiting the CUGBP1 mRNA to processing bodies (P-bodies).[39] Even if the work by Cui et al.[39] describing this regulatory relationship was performed in normal rat intestinal crypt cells, and not in cancer cells, it is noticeable that CUGBP1 is known to play a cancerous role by suppressing $p27^{Kip1}$ in the human breast cancer cell line MCF7 through binding to $p27^{Kip1}$ 5'UTR.[40] Conversely, miR-503 was shown to act as a tumor suppressor via the downregulation of Cyclin D1 in the human head and neck carcinoma cell line UMSCC10B;[41] thus, one might infer that an additional way through which miR-503 plays its tumor suppressor role is by reducing CUGBP1 levels. Additional experiments are surely needed to confirm this hypothesis that would expand our comprehension of CUGBP1 role and modulation in cancer.

A special attention must be devoted to miRNAs, whose action has great consequences in cancer cells as they target Dicer, the RNase III enzyme that processes pre-miRNAs into mature miRNAs.[42] The observation that a global reduction of miRNA abundance appears a general trait of human cancers, playing a causal role in oncogenesis[43,44] well fits with the results by Martello et al.[45] about miR-103 and miR-107 targeting Dicer in breast cancer cells, thus attenuating miRNA biosynthesis and leading to metastasis formation. A relevant issue is raised by the authors of that paper, underlying that the 3'UTR of Dicer mRNA is long and harbors large regions of conservation, unexpectedly, based on its housekeeping nature. As for CPEB2, this feature indicates the need for fine tuning regulation of such proteins, involved in basic mechanisms of cell physiology and pathology. Previously, other authors had described a different miRNA, let-7, targeting Dicer in cancer and non-cancer cells.[46] That result is not in contrast with the miR-103/107 data, but rather confirms that Dicer, just like all key regulators, is subject to fine modulatory mechanisms ensuring a continuously balanced amount, which can be perturbed in several different ways in distinct contexts.

RNA-binding proteins that regulate miRNAs. Because of their chemical nature of ribonucleic acids, miRNAs are obviously regulated by RNA-binding proteins that take part in the general pathways of nuclear and cytoplasmic processing of miRNA precursors in all cell types, Drosha and Dicer.[3] However, in addition to these common players in miRNA biology, some other RBPs specifically act on select miRNAs in defined conditions, such as cancer. A relevant example of such an interaction is miR-20a, whose negative regulation of TGFβR2 and the TGFβ pathway in glioblastoma is greatly enhanced by Quaking (QKI),[47] an RBP behaving as a tumor suppressor in this and other cancer contexts.[48,49] The complex and intriguing situation depicted by Chen et al.[47] shows that p53 induces QKI in glioblastoma, where QKI associates with and stabilizes mature miR-20a, thus inhibiting the TGFβ signaling.

A more general way through which an RBP can regulate miRNA expression in cancer cells is via the modulation of a key enzyme for miRNA production, Dicer. As noted above, cancer cells show a general reduction of miRNA expression,[30,43,44] even if with some relevant exceptions. Thus, the finding that the RBP AUF1, highly expressed in several solid tumors,[50] binds to Dicer mRNA reducing its stability[51] led Gorospe's group to investigate about this in vitro and in vivo, in cancer specimens from human patients. In HeLa cells, they found that AUF1 recognizes several sites along Dicer1 mRNA, both in the 3'UTR and in the coding sequence, and this decreases Dicer production and, in turn, mature microRNA expression. Notably, these authors used cancer tissue arrays to measure Dicer and AUF1 protein levels in tumors and healthy tissues, and found an inverse correlation between Dicer and AUF1 in both groups, where in normal tissues, Dicer expression was high and AUF1 low, and the opposite was true in cancer tissues. This was reproduced in several different types of tumors, e.g., colon, stomach, breast, kidney, liver and pancreas, strongly suggesting that it represents a general feature of human solid tumors and a new, wide-ranging mode of oncogenic action for AUF1.

Another RBP that has been proposed to act as an oncogene is the cold-inducible RBM3, originally discovered to be upregulated in response to mild hypothermia,[52] and then shown to be induced by other kinds of cellular stress, including cancer.[53] Recently,

Pilotte et al.[54] described a mechanism, involving microRNA processing, through which the oncogenic role of RBM3 might be at least in part explained. By using the mouse B104 neuroblastoma cell line as their in vitro model, they demonstrated that RBM3 depletion results in a large downregulation of microRNA expression, in turn likely due to the impairment of pre-miRNP access to Dicer complexes. The authors speculate that their results may unravel one way by which RBM3 acts as an oncogene, i.e., by helping the production of mature "oncomiRs" from the respective pre-miRNAs.

The list of RBPs involved in microRNA processing is much longer, and includes proteins that have been shown to play their roles in in vitro models that are not cancerous ones.[55-58] However, many of those RBPs own demonstrated or proposed roles in oncogenesis,[59,60] and it's easy to infer that part of their action in cancer may be mediated via their ability to modulate miRNA production.

Finally, it's worth mentioning a completely different mechanism evolved by cancer cells to escape microRNA regulation of oncogenes, ultimately leading to the overexpression of oncogenic proteins: alternative cleavage and polyadenylation (APA). It was recently calculated that at least 50% of human genes undergo alternative polyadenylation,[32] leading to transcripts with different 3'UTR sequences, likely exerting differential roles in different contexts. An exhaustive work by Mayr and Bartel studied 27 cancer cell lines from different tissues, together with the normal corresponding tissues, and found that cancer cells used shorter mRNA forms of genes involved in oncogenesis, as compared with the matching normal cells.[61] The shorter forms were generated by APA, thereby preventing microRNA targeting, as microRNA sites were lost following APA. Notably, most of the microRNA sites lost by this mechanism were recognized by tumor-suppressor miRNAs, such as let-7, miR-15 or miR-16, and most of the affected genes were proto-oncogenes. In the same paper, Authors discuss that 3'UTR shortening may very likely affect not only miRNA targeting of oncogenic mRNAs, but also binding by yet undefined RBPs to the same mRNAs. Once more, the frame which is depicted foresees a network of regulators, miRNAs and RBPs, some of which ubiquitous and others cell-specific, that finely tune proto-oncogene expression in normal cells, this balance being disrupted by APA in cancer cells (for an extensive presentation of post-transcriptional regulation focused on 3'UTR, see ref. 62).

HuR: An RNA-binding protein that summarizes all modes of functional interactions with microRNAs. HuR is a well-studied RNA-binding protein that embodies all the features of the RBP/miRNA interplay so far described. HuR is a ubiquitously expressed member of the embryonic lethal and altered vision (ELAV) family of proteins, since long-time known to affect stability and translatability of mRNAs, as first discovered for the HuB member of this family, stabilizing and activating translation of the mRNA encoding glucose transporter 1 (GLUT1).[63,64] HuR consists of three RNA-binding RRM domains, with RRM1 and RRM2 together being responsible for binding to the AU-rich elements (ARE). Although HuR is predominantly a nuclear protein, in response to different types of cellular stress (including cancer), HuR translocates from the nucleus to the cytoplasm, where it modulates the translation and/or stability of many mRNAs.[65]

The functional interplay between HuR and microRNAs was demonstrated for the first time by an elegant study of Bhattacharyya et al.,[66] which showed that the miR-122-mediated repression of CAT-1 translation was reversed by binding of HuR to the ARE of CAT-1 3'UTR. It was further shown that the stress-triggered elevation in cellular HuR facilitated the release of CAT-1 mRNA from P-bodies, suggesting a model whereby HuR and miR-122 associated in a mutually exclusive fashion with the CAT-1 mRNA. Recently, the same authors have investigated the action of HuR on CAT-1 3'UTR whose AREs are positioned at a considerable distance from the miRNA sites, thus unveiling a novel mechanism where the HuR effects lead to the relief of miRNA repression from a distance in a process likely involving HuR oligomerization.[67] Another study evidenced that, in colorectal cancer, the expression of the pro-inflammatory enzyme cyclooxygenase-2 (Cox-2) is negatively regulated by miR-16, and this inhibition is reversed when HuR is overexpressed.[68] Similarly, ERBB-2, a promoter of malignant progression in prostate cancer, is competitively controlled by HuR and miR-331-3p.[69] Moreover, HuR was shown to enhance the cellular abundance of the major chemotherapeutic target TOP2A, once again in competition with a miRNA, miR-548c-3p.[70] TOP2A critically maintains DNA topology after replication and is a key factor governing DNA replication and, consequently, a relevant target in cancer therapy.[71] The authors showed that, in several tumor cells, the antagonistic influence of HuR and miR-548c-3p upon TOP2A expression potently regulates the levels of TOP2A and, hence, the effectiveness of chemotherapeutic agents.

Contrary to what was previously described, other studies illustrated an opposite interaction mode for HuR, as it can cooperate with a miRNA to repress a shared target mRNA. Kim et al. reported that HuR was required both for let-7 to bind the oncogene c-Myc 3'UTR and for let-7 to repress c-Myc expression; on the other hand, let-7 was required for HuR to repress c-Myc expression, as inhibition by HuR was lost after mutating the c-Myc 3'UTR let-7 site.[10] In a manner reminiscent of the HuR/let-7 and c-Myc mRNA, HuR binding to the Ras homolog B mRNA helped the loading of miR-19, an oncogenic component of the miR-17-92 polycistron, and the consequent downregulation of RhoB protein production.[72]

These findings indicate that the differential influence of HuR on many bound transcripts depends on HuR's interplay, either competitive or cooperative, with specific microRNAs, and are supported by the results of recent transcriptome-wide mapping of HuR binding sites in mammalian cells. Those studies revealed that HuR sites are enriched near predicted miRNA sites in mRNAs and frequently overlap with them.[73,74] In this frame, the above cited cases of in vitro relief of miRNA suppression of the CAT1, Cox-2, ERBB-2 and TOP2A mRNAs by HuR, or the cooperation of HuR with let-7 on c-Myc and miR-19 on RhoB can be easily envisaged as specific examples of the general mechanism suggested in references 67 and 68. The same global analyses[73,74] also revealed another intriguing mode of interaction of HuR with

the microRNA regulatory machine: the interaction of HuR with microRNA precursor transcripts (pri-microRNAs). Moreover, the studies found a number of mature microRNAs that are direct targets of HuR, including the oncogenic microRNAs miR-21 and miR-221, and several microRNAs with functional links to HuR activity, as for example, miR-125a and various members of the let-7 family, indicating a possible role of HuR in regulating miRNA expression.

Remarkably, some authors reported that HuR interacts with Ago2 in an RNA-dependent manner.[75] In contrast, others did not detect HuR-Ago2 interaction even in the absence of RNase treatment, whereas HuR appeared to facilitate the targeting of miR-loaded RISC as previously described for Pumilio and miR-221/222.[76] In both cases, anyway, the interaction of HuR with the miRNA machinery suggests that HuR might play a relevant role in miRNA function as regulators of mRNA expression.

In addition, several papers demonstrated that HuR can be modulated by miRNAs. It's the case of miR-519, described in human cervical, colon and ovarian carcinoma cell lines.[77] In all cell lines studied, miR-519 expression significantly reduced cell proliferation in a HuR-dependent way. The novelty of that work did not simply reside in the finding of a microRNA regulating an RBP, but also in the observation that the functional sites in HuR mRNA targeted by miR-519 were located one in a "canonical" 3'UTR position, and another one inside the coding sequence (CDS) of HuR mRNA; furthermore, the site in the CDS resulted to be the most effective in reducing HuR levels. The translational importance of these findings was further corroborated by a work from the same group, showing that HuR and miR-519 levels were inversely correlated in cancer specimens of ovary, lung and kidney, where HuR protein (but not mRNA) levels were significantly increased in cancer samples as compared with the corresponding healthy tissues, and miR-519 was reduced in all cancers vs. healthy controls.[78] Notably, another example of a miRNA likely acting as a tumor suppressor by targeting HuR is that of miR-125a.[79] The authors assayed several breast carcinoma cell lines and found that HuR protein levels and miR-125a expression were inversely correlated; they demonstrated that miR-125a targeted HuR via a single site in HuR 3'UTR, thus inhibiting cell proliferation and migration, while promoting apoptosis. Interestingly, HuR mRNA 3'UTR is 4,910-nt long, downstream of a CDS shorter than 1,000 nt, likely indicating an important role of that region for post-transcriptional regulation, such as that played by miRNAs. It is intriguing to observe that key post-transcriptional fine tuners, like HuR, are themselves regulated at the same level, as already underlined for CPEB2 and Dicer.

Concluding Remarks

Despite the list of miRNA-RBP interactions presented here appears rich, our comprehension of this kind of functional relationship is a relatively recent one, and still in its first steps. In addition, the consequences of the disregulation of molecules often behaving as ubiquitary, like RBPs, in the specific context of human cancer remains an open field for investigation. This is especially true when considering the multifactorial nature of the regulatory networks, where a fine modulation of one component may cause great consequences on another one, and subsequently perturb a balance.

The sensitivity and complexity of such balances makes it often impossible to neatly classify RNA-binding proteins into oncogenic or tumor-suppressor ones, as well exemplified by the case of Pumilio that behaves as a proliferative factor when it cooperates with miR-221/222 to downregulate $p27^{Kip1}$,[16] while it plays a tumor-suppressor role when it enhances miRNA regulation of E2F3 in bladder carcinoma.[17] The case of CUGBP1 is equally representative, as this RBP can downregulate the cell cycle inhibitor $p27^{Kip1}$ by binding to its 5'UTR,[38] but it can also repress, synergistically with miR-222, the translation of CDK4.[80] One of the major challenges that is now proposed to the scientific community studying the molecular basis of cancer is the comprehension of these networks characterized by such a high level of complexity, to explain how a protein (or even a microRNA) can have opposite effects on cancer cell growth depending on the context.

In conclusion, the overall vision that we aim to provide by this review is that a mature mRNA molecule encoding for a cancer-related protein, once in the cytoplasm, far from having an irreversibly determined fate, may still meet several regulators, miRNAs and RBPs, that will finely tune the production of the protein, in a variety of possibilities that as far as 10 y ago we couldn't even suspect.

We surely need to obtain a deeper comprehension of such intricate networks to have the chance of understanding and, thus, fighting cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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