European Journal of Cell Biology 98 (2019) 94–102

Contents lists available at ScienceDirect

European Journal of Cell Biology

journal homepage: www.elsevier.com/locate/ejcb

Review

Characteristics of the competition among RNAs for the binding of shared miRNAs

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ARTICLE INFO

Keywords:
miRNAs
Sponge effect
RNA-RNA crosstalk
Shared MREs
Competing endogenous RNAs
ceRNETs

ABSTRACT

Competing endogenous RNAs (ceRNAs) are RNAs that share common miRNA binding sites and compete with each other for the miRNA association at these sites. The observation of this phenomenon in the cells altered the view of the miRNA target RNAs from molecules that are passively controlled by miRNAs to molecules that also modulate the miRNAs activity. In this review, we build a general profile of ceRNAS characteristics in order to facilitate ceRNAs identification by researchers. The information summarized here contains an actualized list of previously reported ceRNAs and classes of RNAs that can participate in this type of interaction, the expression behavior and characteristics of ceRNAs and miRNAs in the context of competition, the influence of the shared MREs/miRNAs numbers and the miRNA binding strength on the competition, reports on competition between RNAs in different subcellular localizations and the concept that ceRNAs may form a huge regulatory network in the cell.

1. Introduction

Gene expression is strictly controlled at different levels and by different mechanisms in the cells. One of those mechanisms has as central molecules the microRNAs (miRNAs), which are ~22-nucleotide-long RNAs that are endogenously expressed and involved in post-transcriptional gene silencing (Lee et al., 2002). miRNAs perform their biological role in association with the protein Ago2, as part of the RNA-induced silencing complex (RISC), where they act as guides, localizing the target RNAs through base pairing (Maniataki and Mourelatos, 2005). Once paired with the target, RISC is able impose two different fates to the bound mRNA: degradation or translation repression (Eulalio et al., 2008).

For years, the effects of the interaction between miRNAs and their targets were thought to be unidirectional (miRNA → target). The first evidence that challenged this idea came from plants, in a phenomenon termed target mimicry (Franco-Zorrilla et al., 2007). It was observed in *Arabidopsis thaliana* under phosphate starvation conditions, where both the non-coding RNA Induced by Phosphate Starvation 1 (IPS1) and miR-399 were expressed. IPS1 was shown to sequester miR-399, which caused the derepression of the mRNA coding for PHO2, a protein involved in phosphorous response and whose mRNA is also a target of miR-399 (Franco-Zorrilla et al., 2007).

In this sense, target RNAs are far from being passive substrates of miRNAs. In contrast, targets also exert an effect on miRNAs, influencing their availability to act on RNAs (Poliseno et al., 2010; Tay et al., 2011). Based on this concept, in 2011, a new layer of gene expression control was hypothesized (Salmena et al., 2011). The proposed regulatory mechanism relies on the idea that different targets may compete for the association to their miRNAs, modulating the miRNAs silencing activity. Termed competing endogenous RNAs (ceRNAs), those molecules share miRNA response elements (MREs) with other co-expressed RNAs and act as miRNAs sponges, leaving the mRNAs targets free to be translated into proteins (Salmena et al., 2011).

Abbreviations: ASceRNAs, alternative splicing-coupled competing endogenous RNAs; ceRNAs, competing endogenous RNAs; ceRNETs, ceRNA networks; circRNAs, cirular RNAs; IPS1, induced by phosphate starvation 1; miRNAs, microRNAs; MREs, microRNA response elements; RISC, RNA-induced silencing complex

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https://doi.org/10.1016/j.ejcb.2019.04.001
Received 14 January 2019; Received in revised form 1 April 2019; Accepted 3 April 2019

Although many studies have been performed since the ceRNA hypothesis proposition, most of the information about the characteristics of this mechanism is still sparse in the literature. Also, many reviews about ceRNAs have been written, but they generally focus on describing types of molecules acting in the competition and the already investigated and established ceRNAs (Ebert and Sharp, 2010; Gupta, 2014; Kartha and Subramanian, 2014; Tay et al., 2014). This review covers the literature describing these interactions and summarizes some characteristics common to the ceRNAs already reported. In this way, the aim of this article was to build a general profile of ceRNAs characteristics in order to facilitate their identification by researchers. The information summarized here contains (i) an actual list of ceRNAs already reported for humans and the classes of RNAs which that can participate in this type of interaction, (ii) the expression behavior and characteristics of ceRNAs and miRNAs in the context of competition, (iii) the influence of the shared MREs/miRNAs numbers and the miRNA binding strength on the competition, (iv) reports on competition between RNAs in different subcellular localizations and (v) the concept that ceRNAs may form a huge regulatory network in the cell.

2. RNAs acting as ceRNAs

Since the ceRNA hypothesis in 2011, several RNAs were reported to act as competing endogenous RNAs (Poliseno et al., 2010; Tay et al., 2011; Karreth et al., 2015; Yan et al., 2015; Yu et al., 2015a; Wang et al., 2016a). Competition can occur among any RNAs that share MREs for the same miRNAs (Tay et al., 2011). Among all known RNA classes, messenger RNAs (mRNAs), circular RNAs (circRNAs), pseudogenes, long non-coding RNAs (lncRNAs) and natural antisense RNAs (NATs) were already reported to act as ceRNAs (Fig. 1) (Poliseno et al., 2010; Tay et al., 2011; Hansen et al., 2013; Kimura et al., 2015; Wang et al., 2016a). In the case of pseudogenes, the most commonly reported competition interaction is between the pseudogene and its parental gene, mostly due to the high sequence homology of them. This, however, does not preclude pseudogene competition with other gene products (An et al., 2017). In addition, the competition can also occur between a gene spliced isoforms, as reported for OCT4A and OCT4B, both products from of the gene OCT4, or for CDKAL1-v1 and the full-length CDKAL1, both expressed by a homonym gene (Li et al., 2015a; Zhou et al., 2014a). In this case, the involved RNAs have been named alternative splicing-coupled competing endogenous RNAs (AS-ceRNAs) (Zhou et al., 2014a). Table 1 summarizes the human ceRNAs already validated and reported in the scientific literature, together with the biological context where they are important.

3. Characteristics of the competition mechanism

3.1. Expression characteristics of ceRNAs and miRNAs during competition

The main characteristic that indicates whether two RNAs compete for the same miRNA pool is the behavior of the levels of one RNA regarding the experimental expression modulation of the other (Karreth et al., 2015; Tay et al., 2011). Superexpression of one target leads to the upregulation of the other, and its downregulation promotes the partner's downregulation (Karreth et al., 2015). This phenomenon is observed because when the number of molecules of one competitor increases, they titrate away the shared miRNAs, leaving the other RNA free to be translated or to execute its functions (Fig. 2). This is not observed, however, when the cell is depleted for DICER or DROSHA because of the decreased production of miRNAs shared by the competitors (Karreth et al., 2015; Sumazin et al., 2011; Tay et al., 2011). In this case, upregulation of one RNA does not affect the expression of the other (Kartha and Subramanian, 2014; Sumazin et al., 2011; Tay et al., 2011). On the other hand, when silencing the miRNA shared by the competing RNAs, a great improvement in the expression of both RNAs is observed (Kimura et al., 2015). In this case, the experimental modulation of levels of one RNA leads to very small alterations in the expression of its partner because the miRNA that mediates the crosstalk between the RNAs is no longer present (Sumazin et al., 2011; Tay et al., 2011). These last two observations indicate to the researcher that the relationship between the two RNAs is indeed mediated by miRNAs.

In most cases, the crosstalk is reciprocal, as described above (i.e., alterations in the expression of one RNA lead to alterations in the expression of its partner competitor and vice-versa) (Sumazin et al., 2011; Tay et al., 2011). However, there are a few exceptions to this rule, where the competition is not reciprocal (Karreth et al., 2011; Figliuzzi et al., 2013; Yuan et al., 2015; Zheng et al., 2015). This is the case for the ceRNA pair CYP4Z1-CYP4Z2. Upregulation of the CYP4Z2P 3′UTR promotes the expression of CYP4Z1, but superexpression of the CYP4Z1-3′ UTR showed a weaker effect on CYP4Z2P levels (Zheng et al., 2015).

Modulation of the levels of the ceRNAs can possibly also affect the shared miRNA levels. However, there is no consensus in the literature about this issue. Some authors report that alteration of the ceRNAs' expression levels does not alter the miRNA levels in the cell and that the miRNA degradation is not induced after binding to the ceRNA (Deng et al., 2015; Karreth et al., 2011; Zheng et al., 2015). However, some studies show (i) upregulation of the miRNA expression when one of the ceRNAs is downregulated or silenced and (ii) upregulation of the ceRNA promoting reduction in the expression and activity of the miRNA (Su et al., 2016; Wang et al., 2010, 2014).

Indeed, the expression levels of the shared miRNAs and the ceRNAs that compete for them seems to be important for the competition to happen. It was hypothesized that there is minimal competition when the total number of targets largely exceeds the number of miRNA molecules. The competition would also be hampered when the miRNA molecules are much more abundant than ceRNAs (Ala et al., 2013). Moreover, it was shown that the optimal crosstalk between two ceRNAs would occur in a near equimolar state of miRNA and ceRNAs (Ala et al., 2013). In agreement with this observation, it was reported that miRNA:target ratios may influence the competition. Competition seems to occur only for ceRNAs with low total miRNA:target ratios. Targets of highly expressed miRNAs and with high miRNA:target ratios are likely not susceptible to derepression by ceRNA competition. The absence of

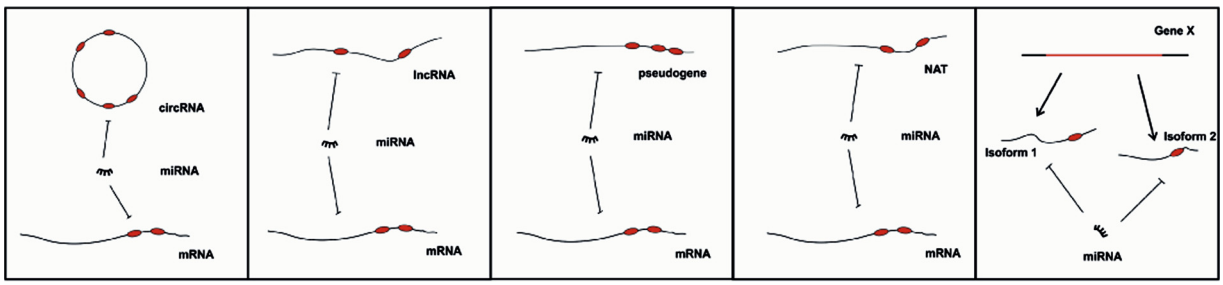

Fig. 1. RNAs already reported to act as competing endogenous RNAs. Red oval shapes symbolize miRNA response elements (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.).

Table 1
List of curated human ceRNAs described in the literature.

Cancer promoters

RNA	mRNA	miRNA	Biological context	Reference
BARD1 9' L	BARD1 isoforms	mirR-203 and miR-101	cancer cells	Pilyugin and Irminger-Finger, 2014
BC032469	hTERT	miR-1207-5p	gastric cancer	Lü et al., 2015
BRAFP1	BRAF	miR-30a, miR -182 and miR-876	lymphoma	Karreth et al., 2015
CCAT1	HMGA2 and c-Myc	let-7	hepatocellular carcinoma	Chen et al., 2016a
CYP4Z2P	CYP4Z1l	miR-211, miR-125a, miR-197, miR-1226 and miR-204	breast cancer	Zheng et al., 2015
H19	FOXM1	miR-342-3p	gallbladder cancer	Wang et al., 2016b
H19	ZEB1 and ZEB2	miR-138 and miR-200a	colorectal cancer	Liang et al., 2015
HMGA1P6 and HMGA1P7	HMGA1	miR-15, miR-16, miR-23b, miR-26a, miR-34b, miR-130b, miR-196a2, miR-326, miR-432, miR-548c-3p, miR-570, miR-603 and let-7a	pituitary tumors	Esposito et al., 2015
HOTAIR	CCND1	miR-1	esophageal cancer	Ren et al., 2016□
HOTAIR	HER2	miR-331-3p	gastric cancer	Liu et al., 2014
HOTAIR	MAPK1	miR-1, miR-214-3p, and miR-330-5p	epithelial ovarian cancer	Yiwei et al., 2015
HOTAIR	PIK3R3	miR-214 or miR-217	ovarian cancer	Dong and Hui, 2016
HULC	PRKACB	miR-372	liver cancer	Wang et al., 2010
KRAS1P	KRAS	miR-143 and let-7 family	prostate cancer cell line	Poliseno et al., 2010
lncARSR	AXL and c-MET	miR-34 and miR-449	renal carcinoma	Qu et al., 2016
lncRNA-ATB	ZEB1 and ZEB2	miR-200a, miR-200b and miR-200c	hepatocellular carcinoma	Yuan et al., 2014
Linc00152	ERBB4	miR-193a-3p	colon cancer	Yue et al., 2016
Malat1	ANXA2 and KRAS	miR-206	gallbladder cancer	Wang et al., 2016c
Malat1	MCL-1	miR-363-3p	gallbladder cancer	Wang et al., 2016a
Malat1	MMP14 and Snail	miR-22	malignant melanoma	Luan et al., 2016
Malat1	ZEB2	miR-200c	kidney carcinoma	Xiao et al., 2015
NEAT1	E2F3	miR-377-3p	non-small cell lung cancer	Sun et al., 2016
OCT4B	OCT4A	miR-335, miR-20a, miR-20b, miR-106a and miR-106b	invasive breast, prostate and colon cancer	Li et al., 2015a
OCT4-pg4	OCT4	miR-145	hepatocellular carcinoma	Wang et al., 2013a, 2013b
PIK3C2A	CD151	miR-124	hepatocellular carcinoma	Liu et al., 2016b
SNHG6-003	TAK1	miR-26a and miR-26b	hepatocellular carcinoma	Cao et al., 2016
SNHG6	ZEB1	miR-101-3p	hepatocellular carcinoma	Chang et al., 2016
TUG1	POU2F1	miR-9-5p	osteosarcoma	Xie et al., 2016
UCA1	MMP14.	miR-485-5p	ovarian cancer	Yang et al., 2016
UCA1	SOX4	miR-204	esophageal cancer	Jiao et al., 2016□
Versican V0 and V1 isoforms	CD34, and fibronectin	miR-133a, miR-199a-3p, miR-144, and miR-431	hepatocellular carcinoma	Fang et al., 2013

Cancer inhibitors

RNA	mRNA	miRNA	Biological context	Reference
CASC2	PIAS3	miR-18a	colorectal cancer	Huang et al., 2016
Cir-ITCH	ITCH	miR-7, miR-17 and miR-214	esophageal squamous cell carcinoma	Li et al., 2015b
CNOT6L	PTEN	miR-17, miR-19a, miR-19b, miR-20a, miR-20b, and miR-106b	prostate and colorectal cancer cell lines	Tay et al., 2011
CTNNAP1	CTNNA1	miR-141	colorectal cancer	Chen et al., 2016b
FER1L4	RB1	miR-106a-5p	gastric cancer	Xia et al., 2014
FER1L4	PTEN	miR-106a-5p	gastric cancer	Xia et al., 2015
FOXO3P and circ-FOXO3	FOXO3	miR-22, miR-136-3p, miR-138, miR-149-3p, miR-433, miR-762, miR-3614-5p and miR-3622b-5p	breast carcinoma	Yang et al., 2015
lncRNA-BGL3	PTEN	miR-17, miR-93, miR-20a, miR-20b, miR-106a and miR-106b	chronic myeloid leukemia	Guo et al., 2014
Linc-223	IRF4	miR-125-5p and	acute myeloid leukemia	Mangiavacchi et al., 2016
MEG3	Bcl-2	miR-181a	gastric cancer	Peng et al., 2015
PTENP1	PTEN	miR-19b, miR-20[a] and miR-21	prostate cancer cell line and oral squamous cell carcinoma	Poliseno et al., 2010; Gao et al., 2016
RB1	PTEN	32 shared miRNAs	glioblastoma	Sumazin et al., 2011
SERINC1	PTEN	Not mentioned	prostate and colorectal cancer cell lines	Tay et al., 2011
VAPA	PTEN	miR-17, miR-19a, miR-20a, miR-20b, miR-26b, miR-106a, and miR-106b	prostate and colorectal cancer cell lines	Tay et al., 2011
ZEB2	PTEN	miR-25, miR-92a, miR-181, and miR-200b	melanoma	Karreth et al., 2011

Other pathologies

RNA	mRNA	miRNA	Biological context	Reference
CDKAL1-v1	CDKAL1	miR-494	type 2 diabetes	Zhou et al., 2014a
circRNA-CER	MMP13	miR-136	osteoarthritis	Liu et al., 2016a
DKK1	PTEN	miR-217, miR-33a, miR-33b, miR-103a, miR-93, and miR-106a	diabetic cardiomyocytes	Ling et al., 2013
GAS5	p27	miR-222	liver fibrosis	Yu et al., 2015a

(*continued on next page*)

Table 1 (*continued*)

Other pathologies				
RNA	mRNA	miRNA	Biological context	Reference
H19	AQP3	miR-874	Intestinal barrier function	Su et al., 2016
Malat1	Rac1	miR-101b	liver fibrosis	Yu et al., 2015b
MEG3	12/15-LOX	miR-181b	cerebral ischemic infract and in hypoxia-induced neuron apoptosis.	Liu et al., 2016c
MIAT	VEGF	miR-150-5p	diabetic retinopathy	Yan et al., 2015

Organs				
ciRS-7	Not mentioned	miR-7	brain	Hansen et al., 2013
Sry	Not mentioned	miR-138	testis	Hansen et al., 2013

Stem and differentiated cells				
RNA	mRNA	miRNA	Biological context	Reference
CARL	PHB2	miR-539	cardiomyocytes	Wang et al., 2014
FLJ11812	ATG13 and CDC20B	miR-4459	vascular endothelial and embryonic stem cells	Lu et al., 2015
IFN-α1 AS, IFN-α and IFN-α AS	IFN-α1	miR-1270	Human Namalwa B cells	Kimura et al., 2015
H19	β-catenin	miR-141 and miR-22	osteoblast differentiation	Liang et al., 2016
H19	DICER	let-7	PA-1 cells	Kallen et al., 2013
linc-MD1	MAML1 and MEF2C	miR-133 and miR-135	myoblasts	Cesana et al., 2011
lincRNA-RoR	Oct4, Sox2, and Nanog	miR-145	embryonic stem cells	Wang et al., 2013a, 2013b
Malat1	SRF	mirR-133	myocyte differentiation	Han et al., 2015

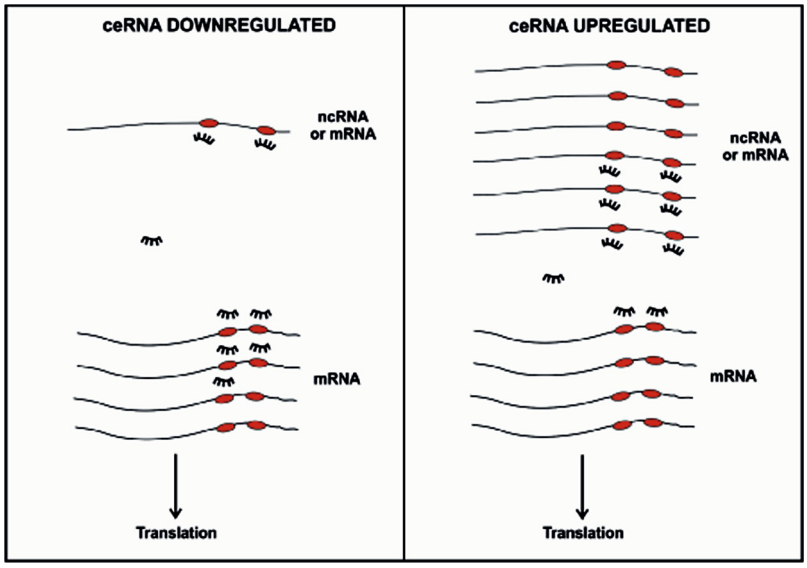

Fig. 2. In the competition between two RNAs for the for the binding of a miRNA, the expression modulation of one RNA leads to the modification of the expression of the other.

Table 2
RNAs that compete with each other for miRNA binding are generally positively correlated.

ceRNAs	Cell type	r value	p value	Reference
BRAF and BRAFP1[a]	diffuse large B cell lymphoma primary tumors	0.42	0.017	Karreth et al., 2015
BRAF and BRAFP1[a]	diffuse large B cell lymphoma cell lines	0.57	0.0029	Karreth et al., 2015
CTNNA1 and CTNNAP1[b]	colorectal cancer	0.631	< 0.001	Chen et al., 2016b
HER2 and HOTAIR[c]	gastric cancer	0.861	Not supplied	Liu et al., 2014
HMGA1 and HMGA1P6[c]	growth hormone tumors	0.859	< 0.0001	Esposito et al., 2015
HMGA1 and HMGA1P7[c]	growth hormone tumors	0.677	< 0.0001	Esposito et al., 2015
KRAS and KRAS1P [c]	prostate cancer	0.486	0.,0408	Poliseno et al., 2010
OCT4 and OCT4-pg4[a]	hepatocellular carcinoma	0.839	0.0001	Wang et al., 2013a, 2013b
PIAS3 and CASC2[b]	colorectal cancer	0.662	< 0.01	Huang et al., 2016
PTEN and PTENP1[c]	prostate cancer	0.754	< 0.0001	Poliseno et al., 2010
ZEB2 and MALAT1[c]	renal cancer	0.622	< 0.0001	Xiao et al., 2015

[a] Pearson correlation.
[b] Logistic regression analysis.
[c] Bivariate correlation analysis through a method not specified.

competition is probably due to the buffering capacity provided by the high miRNA concentrations (Bosson et al., 2014).

Although the optimal crosstalk happens when the ceRNA and miRNA numbers of molecules are approximately equal, reports show that the levels of each RNA of a ceRNA pair do not need to be the same. VAPA, one of the RNAs that competes with PTEN, is expressed at higher levels than PTEN in several cell lines (Ala et al., 2013). Apparently, some ncRNAs can act as competitors even when they are less expressed than their RNA pair. That is the case of the pseudogene BRAFP1, which acts as the ceRNA of BRAF (Karreth et al., 2015). The same occurs with CYP4Z1 and CYP4Z2P, where the pseudogene is less expressed than CYP4Z1 (Zheng et al., 2015). In addition, both RNAs also compete with CDK3 and are also less expressed than this gene (Zheng et al., 2016). FOXO3 shares MREs with FOXO3P and circ-FOXO3. Both ncRNAs effectively compete with FOXO3 for miRNA binding. FOXO3, however, is much more highly expressed than the two ncRNAs (Yang et al., 2015). Although the competition happens in the situations above, the effect of loss of one partner is greater when both RNAs are present in similar quantities (Ala et al., 2013).

Moreover, the expression of both RNAs is generally positively correlated (Table 2), and this characteristic has been used as a one of the criteria for predicting putative ceRNAs (Paci et al., 2014; Welch et al., 2015; Xia et al., 2014). The number of shared miRNAs seems to influence the correlation, as co-expression increases with the number of shared miRNAs (Xu et al., 2015). In addition, a significant negative correlation between miRNAs and ceRNAs was reported (Huang et al., 2016; Liu et al., 2014; Su et al., 2016; Sun et al., 2016). Some articles use the negative correlation of RNA pairs with their respective miRNAs as a filtering criterion in the ceRNA prediction methodology (Zhou et al., 2014b). However, the ceRNA expression is not always negatively correlated with miRNA expression. In some cases, the negative correlation is low or even not significant (Sumazin et al., 2011; Wang et al., 2013a, 2013b; Wang et al., 2016a).

3.2. miRNAs shared by the ceRNAs

3.2.1. Influence of the number of shared miRNAS and MREs

The crosstalk between ceRNAs is mediated by miRNAs, specifically by the miRNA response elements (MREs). The number of shared miRNAs between ceRNAs is variable: BRAFP1 and BRAF bind at least three miRNAs, whereas the competition between PTEN and RB1 is mediated by 32 miRNAs (Karreth et al., 2015; Sumazin et al., 2011). However, the effect of ceRNA expression modulation on its partner depends on how many common miRNAs the two RNAs share. In an computational simulation, increasing ceRNA expression had major effects on RNAs whose number of common binding miRNAs was high compared with RNAs with low numbers of shared molecules. In this last case, the alteration of the ceRNA partner expression was mild, closer to the effect on RNAs with no miRNAs in common (Ala et al., 2013). Therefore, the competition is more pronounced among RNAs that share a large number of miRNAs (Ala et al., 2013).

In addition, when the number of shared miRNAs is large, the effect of expression modulation of one miRNA on its target can be negligible. In other words, target regulation is unlikely to be significantly affected when only one miRNA has its expression altered (Sumazin et al., 2011).

In addition, the number of MREs of the shared miRNA can be variable in each RNA of the pair. This means that one ceRNA can have more MREs for a given shared miRNA than its partner, and this difference may influence the derepression levels by one ceRNA over another. The derepression occurs even when the competitor has less MREs than its partner. However, both the competition and the derepression are improved with the addition of MREs in the competitor sequence (Yuan et al., 2015).

3.2.2. Influence of miRNA binding characteristics

The ceRNA regulation efficiency is not only determined by the number of shared miRNAs or MREs; the binding strength between mRNA and miRNA also has an influence on the competition (Yuan et al., 2015). Evidence of this fact includes a study on ceRNAs applying synthetic gene circuits, which showed that the higher the MRE-miRNA binding affinity, the stronger was the ceRNA effect (Yuan et al., 2015). Moreover, the level of complementarity proved to also be important. When miRNAs incompletely bind to the MREs of the ceRNA pair, increasing the expression of one of the RNAs caused improvement in the expression of its partner RNA. However, when one of the ceRNAs has MREs that bind perfectly to the miRNAs, modulation of its expression did not influence the expression of its pair (Yuan et al., 2015). In this case, nonreciprocal competition was observed (Yuan et al., 2015).

In addition, there is a hierarchy of the miRNA binding to the MREs on the targets. miRNAs bind preferentially to the high affinity 8- and 7-mer seed sites (Bosson et al., 2014). This miRNA behavior leads to the occurrence of two different target binding situations: (i) when the miRNA expression is lower than the target site pool, these molecules will bind to 8- and 7-mer sites first; however, (ii) when the miRNA expression is increased, the interactions also spread to the 6-mer seed sites (Bosson et al., 2014). This characteristic influences the size of the competitor pool. In the case of low miRNA expression, the competitors pool is small and it is restricted to the high- affinity sites. However, when the miRNA levels are high, the pool is larger and the miRNAs will also bind to the low-affinity sites. In this last case, the target pool may become too large to be influenced by alterations in the expression of one ceRNA (Bosson et al., 2014).

Another miRNA binding characteristic is the interaction position on the RNA. In mRNAs, the majority of miRNAs binds to the 3′ UTR sequence. This is not necessarily true for ncRNAs and the MREs can be located in the middle of the molecule (Wang et al., 2013a, 2013b). Moreover, different levels of miRNA interaction could occur among different sites for the same miRNAs in a target. The lncRNA CCAT1 has three sites for miR-155; however, only one of the sites seems to have a strong interaction with the miRNA (Chen et al., 2016a). In addition, some authors observed that the predicted ΔG of the miRNA-lncRNA binding was lower than the ΔG of the miRNA-mRNA association (Cesana et al., 2011).

3.3. Subcellular localization

The different elements that participate in the competition (mRNAs, lncRNAs, pseudogenes, circRNAs and miRNAs) can naturally be found in different subcellular localizations (Liao et al., 2010; Cabili et al., 2015; Venø et al., 2015; Yan et al., 2015). However, for the competition to occur, both ceRNAs and miRNAs must share the same compartmental location in the cell. Many authors indeed support the opinion that there must be an overlap in the cellular localization of the miRNAs and ceRNAs involved in a given competition relationship (Salmena et al., 2011; de Giorgio et al., 2013; Tay et al., 2014; Qu et al., 2016). Thus, the knowledge of this cellular distribution information is very important when one proceeds with a ceRNA crosstalk prediction.

Nevertheless, evidence shows that RNAs that do not share the same subcellular compartment but do share miRNA target sites are not impeded to compete between each other. The competition may happen when the shared miRNAs are found in both ceRNAs' regions. The lncRNA MALAT1 is found in the cytoplasm, but it is predominantly located in the nucleus. Its location, however, does not impair its ceRNA activity on its partner, ZEB2, which is cytoplasmatic. In addition, miR-200c, a miRNA whose binding site is shared by both RNAs, is found in the cytoplasm and the nucleus of the cell used in the study (Xiao et al., 2015). The same is observed for MIAT and lncRNA-BGL3. MIAT is a nuclear lncRNA that acts as a ceRNA of VEGF. The miRNA shared by both RNAs is found in the cytoplasm and cell nucleus, and it associates with MIAT in the nucleus (Yan et al., 2015). LncRNA-BGL3, in your turn, acts as a ceRNA of PTEN, and it is found in both the nucleus and cytoplasm (Guo et al., 2014).

4. ceRNA Networks: the ceRNETs

Most of the articles describing ceRNAs reports this type of interaction between only two molecules (Liu et al., 2014; Peng et al., 2015; Yu et al., 2015b; Wang et al., 2016a; Sun et al., 2016). However, in the real cell context, the competition is certainly not restricted to only two RNAs. It probably occurs among several RNAs, forming a network named ceRNET (Kimura et al., 2015; Salmena et al., 2011; Sumazin et al., 2011; Zheng et al., 2016). The complexity that a ceRrNET can achieve is evidenced by the work of Sumazin et al. (2011), which predicted that, in glioblastoma cells, approximately 248,000 pairwise RNA-RNA interactions are mediated by shared miRNAs, with a highly conservative false discovery rate (Sumazin et al., 2011). Indeed, it has been speculated that the ceRNA layer of regulation may be as large as transcriptional regulation in terms of size (Sumazin et al., 2011).

Although most ceRNAs are investigated in pairs, some competition networks are starting to be unraveled. One of the ceRNETs that has continuously received new nodes is the PTEN network, indicating that PTEN may be strongly regulated by ceRNAs. This fact is illustrated by a ceRNET constructed based on glioblastoma data, where PTEN showed a total of 534 interactions. Among the genes that may modulate PTEN levels are ABDHD13, CTBP2, HIAT1, HIF1A, KLF6, NRAS, RB1, TAF5 and TNKS2, aside from the known drivers of glioma tumorigenesis and glioblastoma subtypes PDGFRA, RUNX1, STAT3 and VEGFA (Sumazin et al., 2011). Other PTEN ceRNAs already described can be accessed in Table 1.

There is also crosstalk among ceRNETs and transcription factors (TF). One of these competition networks includes CYP4Z1, its pseudogene CYP4Z2P and CDK3. CYP4Z1 and CYP4Z2P compete with each other for the association of hsa-miR-125a-3p, regulating ERα activity (Zheng et al., 2015, 2016). This regulation, however, is not direct. CYP4Z1 and CYP4Z2P also act as ceRNAs of CDK3, which phosphorylates ERα, promoting its transcriptional activity. As a result of this interaction network, the Erα target genes c-Myc, Cyclin D1 and TFF1 are upregulated (Zheng et al., 2016). The lncRNA HULC also integrates a small ceRNET that involves a TF. HULK competes with the mRNA from the PRKACB gene for the binding of miR-372. PRKACB in turn promotes the phosphorylation of CREB, which binds the HULK promoter and induces its transcription (Wang et al., 2010).

Beyond the small networks reported above, large-scale ceRNETs has also been constructed and analyzed, together with the proposition of computational methods to build them (Nitzan et al., 2014; Paci et al., 2014; Xu et al., 2015; Zhou et al., 2014b). These cerRNETs may be very useful to understand the crosstalk among ceRNAs in the whole cell context. In fact, experiments showed that the modulation of one element of a the ceRNET can cause a propagated perturbation effect on the network. The introduction of a synthetic target for one of the network miRNAs (named here as X) promoted an elevation of the endogenous target levels. This observation is an expected result, as the synthetic target probably acted as a ceRNA. Interestingly, levels of mRNAs that are not targets of X, but share other miRNA target sites with mRNAs targeted by X, also increased (Nitzan et al., 2014). This is clear evidence of crosstalk between distant ceRNAs in the network.

In addition, the studies aiming to find new drug therapy targets and predictive or prognostic cancer markers may also benefit from the construction of large-scale ceRNETs. Comparison of ceRNETs from normal and cancerous cells showed that the miRNA-mediated interactions change completely from one condition to another (Paci et al., 2014). ceRNETs for 20 cancer types revealed that cancers originated from similar tissues share common ceRNAs. In addition, ceRNA interactions common to the 20 cancer types studied were also detected (Xu et al., 2015). Moreover, supporting the usefulness of ceRNETs in cancer research, the analysis of one breast-cancer-specific ceRNA network encountered 12 hub genes with strong metastasis prediction potential (Zhou et al., 2014b).

The network characteristics of mRNAs ceRNETs have also been studied. An experimentally determined network, including the miRNAs and the mRNAs that compete for them, showed a scale-free topology that is a characteristic of most biological networks, and its nodes are highly interconnected (Nitzan et al., 2014).

The studies described above clearly show a movement of the ceRNA research towards large-scale investigations. However, the large-scale networks already reported were constructed with only mRNAs or mRNAs and lncRNAs. A more realistic ceRNET should also include other RNAs that can act as competitors, such as pseudogenes and circRNAs.

5. Conclusions

The study of competing endogenous RNAs is a young research area, and the knowledge about this mechanism is still sparse in the literature. However, analyzing all of the reported ceRNA cases permitted some conclusions about characteristics that may be universal for this type of RNA-mediated miRNA regulation. The general reciprocal crosstalk between the ceRNAs, their possible influence on the involved miRNAs levels, the impact on competition occurrence and strength of factors such as the ceRNA and miRNA levels, their subcellular localizations, the number of shared miRNAs or MREs, and the characteristics of the miRNA target site, such as seed length, miRNA binding strength and level of complementarity in the miRNA-MRE base pairing, can be highlighted.

Although most of the ceRNA interactions described up to now involve only two competing RNAs, progress in this field indicates that the competition mechanism is organized into networks. The ceRNA field is still in its infancy, but it is clear that a movement towards large-scale investigations will contribute to our understanding of real dimension and importance of this new level of gene expression regulation. In this sense, the advance in the research areas for ncRNAs, to unraveling unknown nodes and connections, and on methods of competitors network construction and analysis will probably reveal important biological information on the role of ceRNA in cells.

Author disclosure statement

No competing financial interests exist.

Acknowledgment

This work was supported by the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) under Grant 301149/2012-7.

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