CeRNA Networks in Neurodegenerative Diseases

Subjects: Biochemistry & Molecular Biology

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Protein aggregation is classically considered the main cause of neuronal death in neurodegenerative diseases (NDDs). However, increasing evidence suggests that alteration of RNA metabolism is a key factor in the etiopathogenesis of these complex disorders. Non-coding RNAs are the major contributor to the human transcriptome and are particularly abundant in the central nervous system, where they have been proposed to be involved in the onset and development of NDDs. Interestingly, some ncRNAs (such as lncRNAs, circRNAs and pseudogenes) share a common functionality in their ability to regulate gene expression by modulating miRNAs in a phenomenon known as the competing endogenous RNA mechanism. Moreover, ncRNAs are found in body fluids where their presence and concentration could serve as potential non-invasive biomarkers of NDDs.

competing endogenous RNAs (ceRNA) neurodegenerative diseases (NDDs) extracellular/circulating biomarkers microRNA long non-coding RNA circular RNA pseudogene mRNA ceRNA network (ceRNET) RNA editing

1. Introduction

ncRNAs can be classified into two groups according to their length: small ncRNAs (<200 nucleotides) and long ncRNAs (>200 nucleotides) [1]. Among small ncRNAs, microRNAs (miRNA) stand out, being around 22 nucleotides long and regulating gene expression at the post-transcriptional level in a sequence-specific manner [2]. Approximately 70% of the identified miRNAs are expressed in the brain [3] and have been described as major regulators of neuronal homeostasis, their misregulation being associated with pathological conditions of CNS [2]. The largest class of ncRNAs in the mammalian genome is long ncRNAs (lncRNAs), which can be further grouped into linear RNAs and circular RNAs [1] [4]. Linear lncRNAs (hereon referred to as lncRNAs) are similar to protein-coding messenger RNA (mRNA) in sequence length and transcriptional and post-transcriptional behavior [1]. However, lncRNAs play a different cellular role compared to mRNAs. Moreover, they have been described to be involved in brain development, neuronal function, maintenance and differentiation [5]. Circular RNAs (circRNAs) represent a relatively recently discovered class of RNAs that, unlike linear RNAs, are characterized by a covalent bond that joins the 5′ and 3′ ends and confers increased stability (half-life of 48 h vs. 10 h for mRNAs) [6]. circRNAs are highly abundant in the brain, enriched in synaptoneurosomes and upregulated during neuronal differentiation [7], so they could be promising biomarkers in age-associated NDDs.

On the other hand, a considerable number of pseudogenes can be transcribed to ncRNAs, even though they have historically been regarded as inactive gene sequences [8] [9]. In fact, there is mounting evidence that pseudogenes may modulate the expression of parental as well as unrelated genes [8] [9]. Therefore, alteration of pseudogene transcription could perturb gene expression homeostasis leading to disease [8].

In 2011, Pier Paolo Pandolfi's group proposed the so-called ceRNA hypothesis [10], which sought to explain how RNAs "talk" to each other, establishing interactions that modify functional genetic information and that may play major roles in pathological conditions. This hypothesis is based on the fact that miRNAs can recognize their specific target sites called miRNA response elements (MRE) in different RNA molecules, causing target repression via miRNA-RISC complex-mediated degradation. Thereby, miRNAs could mediate regulatory crosstalk between the diverse components of the transcriptome, comprising mRNAs and ncRNAs, which include pseudogenes, lncRNAs and circRNAs.

In a simplified manner, when two RNA molecules share the same MRE they potentially compete for the same pool of miRNAs. Thus, when the expression of a ceRNA is upregulated, it will bind and titrate more miRNAs (phenomenon called miRNA sponging), leaving fewer miRNA molecules available for binding the mRNA with shared MRE. Hence, this corresponding mRNA will become derepressed. In reverse, when the ceRNA levels are reduced as a consequence of a biological disturbance, the corresponding mRNA will be downregulated due to hyperrepression (Figure 1).

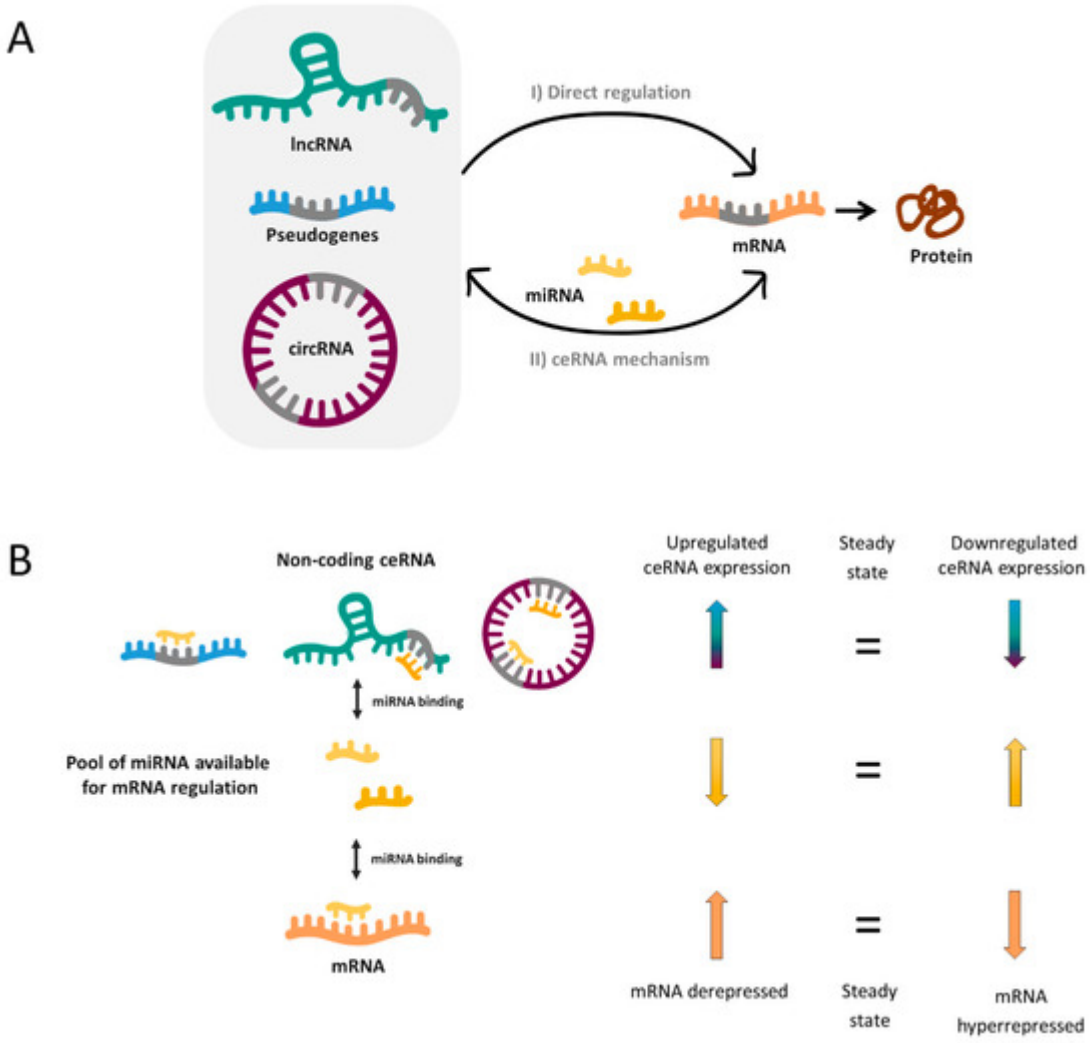

Figure 1. (**A**) Transcriptional and post-transcriptional regulation of messenger RNAs (mRNAs) (orange) can be both influenced by direct and indirect mechanisms involving long non-coding RNAs (lncRNAs) (green), pseudogenes (blue) and circular RNAs (circRNAs) (purple). (I) Direct mechanisms include some processes that act on the transcription rate in the nucleus through the specific RNA-RNA complex and others that help the stability of mRNA molecules in the cytoplasm. (II) Competing endogenous RNA (ceRNA) mechanism is a bidirectional indirect regulation mechanism mediated by microRNAs (miRNAs) (yellow). miRNAs bind lncRNAs, pseudogenes, circRNAs and mRNAs through the miRNA response elements (MRE) (grey). (**B**) ceRNA hypothesis. Upregulation of a certain ceRNA (pseudogene, lncRNA or circRNA) expression can decrease cellular concentrations of the corresponding miRNA, resulting in the de-repression of other transcripts (mRNA) that contains the same MREs (left arrows). Conversely, the downregulation of a certain ceRNA would lead to increased concentrations of specific miRNAs and thus to hyperrepression of mRNA expression (right arrows).

Without doubt, the reality is more complex and a miRNA can bind more than one mRNA (50% of miRNAs are predicted to target 1–400 mRNAs and some of them up to 1000) [11]. Likewise, most ceRNAs contain 1 to 10 MREs [11] and, as a consequence, complex ceRNA networks involving a large number of RNA molecules are established. Novel bioinformatic and computational tools have enabled to elucidate an increasing number of ceRNA networks,

as well as predict the most important enclaves of them. These may provide a valuable global vision to identify new biomarkers, underlying pathways or potential therapeutic targets for complex disorders such as NDDs.

2. ceRNA Networks and Neurodegenerative Diseases

Over the last years, the ceRNA hypothesis has been corroborated by a large number of experiments. However, investigation of ceRNA mechanisms and their interaction networks has been mainly carried out in cancer research [12] [13] [14] [15]. Nevertheless, some advances have also been made in the field of NDDs (Table 1).

Table 1. miRNA-ceRNAs networks experimentally validated associated with NDDs

Disease	ncRNA		miRNA	mRNA	Sample	Ref.
AD	lncRNA	BACE1-AS	miR-29, miR-485, miR-761,miR-124 and miR-107	*BACE1*	Computational analysis from human data and cellular and mouse models	[16]
			miR-214-3p	-		[17]
			miR-132-3p	-		[18]
		XIST	miR-124	*BACE1*	Cellular and mouse models	[19]
			miR-132	-		[20]
		NEAT1	miR-124	*BACE1*	Cellular and mouse models	[21]
			miR-107	-		[22]

		SOX21-AS1	miR-107	-	Cellular model	[23]
		NEAT1 HOTAIR MALAT1	miR-107, miR-103, miR-16, miR-195, miR-15a and miR-15b	*CDK5R1*	Cellular model	[24]
		MALAT1	miR-125b	*CDK5, FOXQ1* and *PTGS2*	Cellular and rat models	[25]
			miR-30b	*CNR1*		[26]
		TUG1	miR-15a	*ROCK1*	Cellular and mouse models	[27]
		SNHG1	miR-137	*KREMEN1*	Cellular model and human primary cell culture	[28]
			miR-361-3p	*ZNF217*		[29]
		lncRNA-ATB	miR-200	*ZNF217*	Cellular model	[30]
		LINC00094	miR-224-4p miR-497-5p	*SH3GL2*	Cellular model	[31]

		MIAT	miR-150-5p	*VEGF*	Cellular and mouse models	[32]
		Rpph1	miR-326	*PKM2*		[33]
			miR-122	*Wnt1*	Cellular and mouse models	[34]
			miR-330-5p	*CDC42*		[35]
		linc00507	miR-181c-5p	*MAPT* *TTBK1*	Cellular and mouse models	[36]
		lnc-ANRIL	mir-125a	*TNF-α, IL1B IL6* and *IL17*	Cellular model	[37]
	circRNA	ciRS-7	miR-7	*UBE2A*	Human brain	[38]
			*miR-7	**NF-Kb/p65*	Cellular models	[39] [40] [41]
		circ_0000950	miR-103	*PTGS2*	Cellular models	[42]
		circHDAC9	miR-138	*Sirt1*	Cellular and mouse models	[43]
			miR-142-5p	-		[44]
PD	pseudogene	*GBAP1*	miR-22-3p	*GBA*	Cellular models	[45]

	lncRNA	SNHG1	miR-153-3p miR-15b-5p miR-7 miR-221/222	*PTEN* *SIAH1, GSK3β* *NLRP3* *CD*KN1B (p27)	Cellular and mouse models	[46] [47] [48] [49] [50]
		HAGLROs	miR-100	*ATG10*	Cellular and mouse models	[51]
		HOTAIR	miR-874-5p	*ATG10*	Cellular and mouse models	[52]
			miR-126-5p	*RAB3IP*		[53]
		NEAT1	miR-212-5p	*RAB3IP*	Cellular models	[54]
			miR-1277-5p	*ARHGAP26*		[55]
			miR-124	-		[56]
		AL049437	miR-205-5p	*MAPK1*	Cellular and mouse models	[57]
		MALAT1	miR-205-	*LRRK2*	Cellular and mouse models	[58]

			5p		
			miR-124	*DAPK1*	[59] [60]
			miR-129	*SNCA* (α-syn)	[61]
		SNHG14	miR-133b	*SNCA*	Cellular and mouse models [62]
		LincRNA-p21	miR-1277-5p	*SNCA*	[63]
			miR-181 family	*PRKCD* (PKC-δ)	Cellular and mouse models [64]
			miR-625	*TRPM2*	[65]
		GAS5	miR-223-3p	*NLRP3*	Cellular and mouse models [66]
		BDNF-AS	miR-125b-5p	-	Cellular and mouse models [67]
		Mirt2	miR-101	-	Cellular model [68]
		lncRNA H19	miR-301b-3p	*HPRT1*	Computational analysis from human data and [69]
			miR-585-3p	*PIK3R3*	cellular and mouse models [70]

	circRNA	*ciRS-7	miR-7	*SNCA*	Cellular and mouse models	[71] [72] [73] [74] [75]
		circSNCA	miR-7	*SNCA*	Cellular model	[76]
		circzip-2	*miR-60	*M60.4ZK470.2, igeg-2* and *idhg-1*	Worm model	[77]
		circDLGAP4	miR-134-5p	*CREB*	Cellular and mouse models	[78]
MS		Gm15575	miR-686	*CCL7*	Cellular and mouse models	[79]
	lncRNA	PVT1	miR-21-5p	*SOCS5*	Cellular and mouse models	[80]
		TUG	miR-9-5p	*NFKB1 (p50)*	Cellular and mouse models	[81]
		HOTAIR	miR-136-5p	*AKT2*	Cellular and mouse models	[82]
		GAS5	miR-137	-	Human blood	[83]
	circRNA	hsa_circ_0106803	*miR-149	**ASIC1a*	Human blood (PMBCs) [88] [89]	[84] [85]

ecules by s suggest regulates neurodevelopment and normal neuronal function, for which some crucial aspects of neurodegenerative diseases may stem from the modification of both coding and non-coding RNA [89] [90] [91].

[88]		hsa_circ_0005402 [92] hsa_circ_0035560	*14 miRNAs (miR-1248, miR-766)	- [93]	Human blood (PMBCs)	[86]
SCA7	lncRNA	lnc-SCA7	miR-124	*ATXN7*	Human samples, and cellular and animal models [96]	[87]

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editing site in an RNA molecule could drastically modify its function, resulting in new or different ceRNA networks that regulate gene expression.

* Experimental validation is needed.

Interestingly, A-to-I editing has been reported specifically reduced in SALS motor neurons due to the progressive downregulation of ADAR2 [97] [98]. Based on this evidence, Hosaka et al. [99] searched for extracellular RNAs with ADAR2-dependent A-to-I sites that may reflect the intracellular pathological process and thus could be potentially good ALS biomarkers. A total of six RNAs were identified. Among these, a circRNA (hsa_circ_0125620, also called circGRIA2) with an ADAR2-dependent site was detected in human SH-SY5Y neuroblastoma cells as well as in their culture medium [99]. Therefore, variations in RNA editing efficiency in ALS, as a consequence of decreased ADAR2 activity, could be potentially measured in peripheral circRNAs and other relatively stable ncRNAs. In light of this evidence, this editing phenomenon may be considered a very important aspect, since it allows obtain relevant information of disease pathological process from non-coding RNAs.

Other NDDs, such as AD and PD, also present alterations in RNA editing patterns [100] [90] [101] [102]. In fact, a recent study has explored how RNA editing in AD contributes to the regulation of AD-related processes in blood cells in two populations of patients [103]. Results identified differentially edited sites predicted to disrupt miRNA target sites in five genes. In all cases, decreased editing was observed in AD suggesting a greater miRNA-binding affinity relative to controls [103]. In light of this evidence, alterations in RNA editing could result in a specific RNA profile, given by different amount of RNAs, modified interaction networks and editing levels or efficiencies changes in A-to-I sites, that could be useful to identify new robust biomarkers of these NDDs (Figure 2).

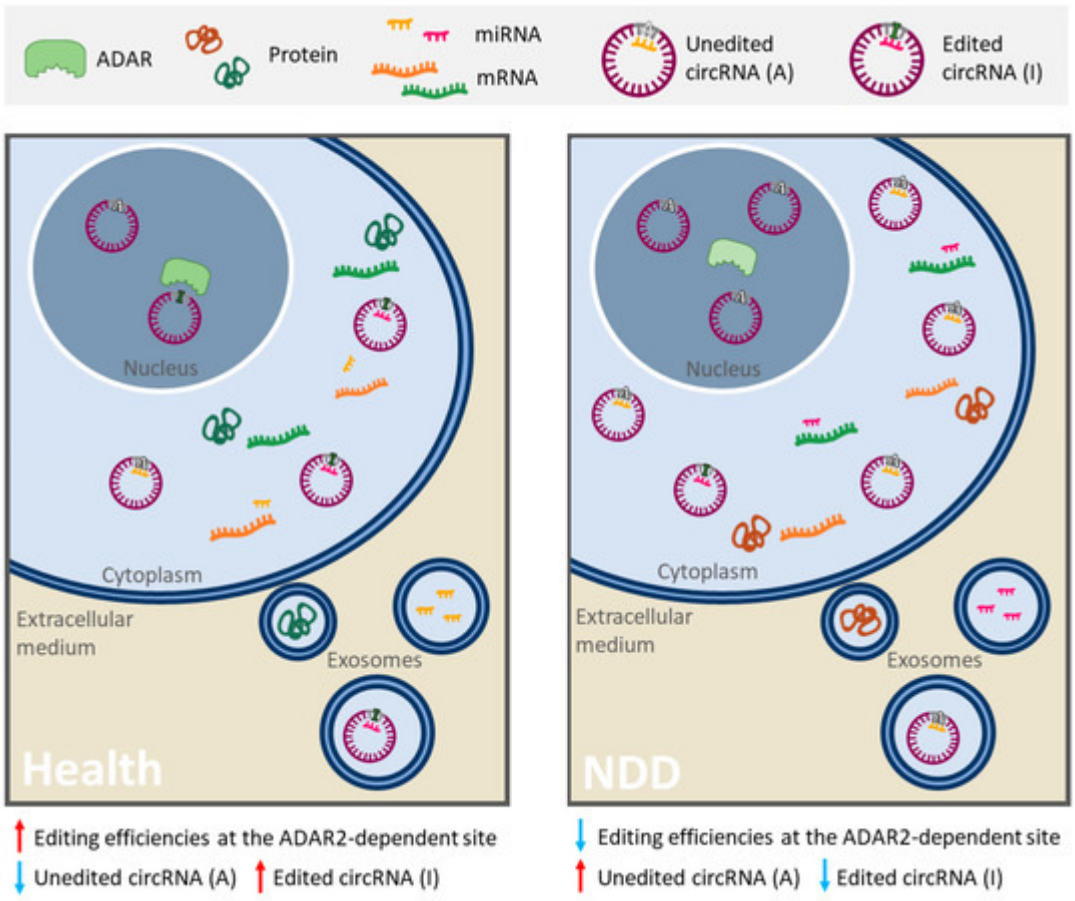

Figure 2. Schematic representation of alterations in RNA editing that could provide a specific RNA profile in neurodegenerative diseases (NDDs). In some linear and circular RNAs, the enzyme ADAR2 deaminates adenosine (A) into inosine (I), resulting in important biological consequences (especially in ncRNAs). On the one hand, a single editing site in MRE or miRNA seed region can drastically change its set of targets. In this image, circ-Purple acts as a miR-Yellow sponge, which regulates the mRNA expression of Orange gene (right panel). Deamination of A into I in circ-Purple could affect its binding site for miR-Yellow. In consequence, circ-Purple stops sponging miR-Yellow, and it may bind to another miRNA (miR-Pink) and promote the expression of Green gene (left panel). Hence, the ceRNA interaction network has changed, emerging a new or different regulatory axis. On the other hand, ADAR editing negatively regulates circRNA biogenesis, resulting in a decrease of circRNA levels (in the left panel there is less circ-Purple expression than in the right panel). In NDDs with a diminution of A-to-I RNA editing (like ALS, AD or PD), a different and opposite profile/pattern could be observed (right panel) with respect to a normal editing efficiency of ADAR (left panel). Therefore, alterations mediated by RNA editing in RNAs and its ceRNA interaction networks may serve as robust biomarkers of these NDDs. This figure is based on a previously published figure [99] [104].

4. Conclusion

The vast majority of NDDs can be definitively diagnosed only after death or in advanced stage, and their previous diagnosis is based on ruling out other possible causes for the symptoms. For most NDDs, there is no cure or

treatment capable of reversing the damage due to neuronal death. Therefore, it is critical to find new biomarkers that would facilitate an early diagnosis, prognosis and efficient monitoring of therapeutic interventions.

In the search for new biomarkers, non-coding RNAs have been proposed as promising tools for diagnosis and prognosis. Many ncRNAs often arise from genes that cause NDDs or are somehow involved in the development of one of these disorders (like BACE1-AS or circSNCA). Thus, ceRNETs established by these ncRNAs could well be, at least in some cases, disease and even stage-specific. However, as reported in this review, ncRNAs are commonly misregulated in several NDDs (Figure 3). This is the case, for example, of the lncRNAs SNHG1 and HOTAIR, which are altered in AD [28] [29] and PD [46] [47] [48] [49] [50], and PD [52] [53] and MS [82], respectively. However, their miRNA targets may vary depending on cell types affected by the disease and, therefore, the mechanism of action may also differ. Similarly, miR-7 has been shown sponged by ciRS-7/CDR1as and circSNCA in AD [38] [39] [40] [41] and PD [76], respectively, being detrimental in the first case and beneficial in the second, due to regulation of different target mRNAs. The apparent discrepancy between the anti and pro cell death activity of miR-7 reflects the complex regulatory role of miRNAs, so further research is required to clarify their function in different cellular and disease contexts.

In this way, by analyzing various elements of the altered ceRNETs, it may be possible to differentiate one NDD from another even if there were common components. Ideally, working with several correlatable molecular targets at the same time (lncRNAs/circRNAs/pseudogenes-miRNA-mRNAs) increases the sensitivity and reliability of ceRNETs as biomarkers. It should be noted that ceRNETs construction also contributes to the identification of new molecular mechanisms of gene regulation that may lead to a better understanding of the etiopathogenesis of the diverse NDDs, as well as to reveal new therapeutic targets and obtain relevant information about the pathological processes of the disease.

In this sense, ceRNETs may also reflect the editing efficiencies of ADAR, a post-transcriptional phenomenon dysregulated in several NDDs. RNA editing can affect the levels and the efficiency of RNA interaction networks, so its alterations could provide a specific RNA fingerprint that helps in the diagnosis or prognosis of NDDs. Finally, the described crosstalk between the RNA molecules in certain ceRNETs is relatively conserved between species, paving the way for translation of data obtained from animal models into clinical practice [105] [106].

Among the main advantages of ceRNETs for biomarker research, the fact that these ncRNAs are easily accessible is noteworthy, since they are extremely stable in circulation and may be detected in exosomes. Such is the case for circRNA CDR1as/ciRS-7 and lncRNA MALAT1, found in exosomes. Interestingly, levels of ciRS-7 in these vesicles depend on the intracellular abundance of the miRNA that it sponges (miR-7) [107]. Furthermore, ciRS-7 and MALAT1 may regulate miRNA expression in target cells after exosomal delivery modulating their phenotype, since these ceRNAs retain their biological activity [107] [108]. Therefore, ciRS-7 and MALAT1 together with other circulating ncRNAs (e.g., NEAT1, GAS5, hsa_circ_061346, hsa_circ_000843) represent promising candidates for peripheral ceRNA biomarkers of NDDs. Although many of the ncRNAs discussed earlier have not been reported in exosomes to date, some of them are predicted to be detected in human blood exosomes by exoRBase (e.g., circSLC8A1,

circCORO1C, SNHG1, BACE1-AS) [109]. Indeed, it has recently been demonstrated that plasma exosomal BACE1-AS levels could serve as a biomarker of AD [110] [111].

Because ceRNA interaction networks are multifactorial, they may represent an advantage in studies of these complex neurodegenerative disorders, one being at the level of biomarkers (combined RNA biomarkers panels) and another at the level of therapeutic targets (modulate the levels of multiple disease-associated RNAs at once by just targeting one).

Nevertheless, it must be taken into account that there is still much to do, since these networks are very complex and their interactions must be experimentally defined [105]. In this sense, some “non-canonical” aspects of ncRNAs have also been described: i) circRNAs that can also sponge or serve as a decoy for RBPs or lncRNAs, ii) miRNAs that may increase the expression of target genes, iii) lncRNAs that can be precursors of smaller ncRNAs and can regulate miRNA and circRNA biogenesis, iv) miRNAs that can direct Ago2 to degrade lncRNA and circRNA, v) lncRNAs that compete with miRNAs for the target site of mRNA, and vi) context-specific miRNA function and target identification [112] [113] [114] [115] [116] [117] [118] [119].

Although the full extent of ceRNA networks still needs to be still determined, the competition of ncRNA and mRNAs for miRNAs constitutes a key point of gene regulation that could underlie some pathological aspects of neurodegenerative diseases, favoring at the end the identification of specific pathological mechanisms for each disease.

Figure 3. Complexity and interaction of ceRNETs in NDDs. The diagram was constructed with Gephi software from ceRNAs (lncRNAs and circRNAs) that, according to the bibliography cited in this review, contribute to the pathogenesis of more than one neurodegenerative disease and miRNAs that are part of ceRNETs from more than one ceRNA. Interactions between RNA molecules are represented with lines colored in accordance with the NDD background they have been described in: spinocerebellar ataxia type 7 (SCA7) (red), Alzheimer's disease (AD) (purple), Parkinson's disease (PD) (blue), multiple sclerosis (MS) (yellow) and amyotrophic lateral sclerosis (ALS) (green).

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