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The Emerging Field of Noncoding RNAs and Their Importance in Pediatric Diseases

Rui Zhou, PhD[1,2,3], **Piyush Joshi, PhD**[1,3,*], **Keisuke Katsushima, PhD**[1,3,*], **Weihong Liang, PhD**[1,2,3], **Wei Liu, PhD**[1,2,3], **Neil A. Goldenberg, MD, PhD**[4,5], **George Dover, MD**[4], **Ranjan J. Perera, PhD**[1,3]

[1]Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD

[2]Department of Biological Chemistry, Johns Hopkins University School of Medicine, Baltimore, MD

[3]Johns Hopkins All Children's Hospital Institute for Fundamental Biomedical Research, St. Petersburg, FL

[4]Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD

[5]Johns Hopkins All Children's Institute for Clinical and Translational Research, St. Petersburg, FL

Dr Barton Childs' landmark 1999 text, *Genetic Medicine – A Logic of Disease*, led to the development of a new curriculum at Johns Hopkins School of Medicine entitled "Genes to Society."[1] A core part of contemporary medical school and pediatric residency training is individualized medicine. Trainees are now being equipped for an era of personalized, "precision" medicine. Childs said that, in the next century, medicine will be focused on the treatment of individuals rather than disease. This raises the question of how different are individuals at the genomic level? Early after the discovery of the genetic code, it was recognized that some 3 million single nucleotide polymorphisms could be used to distinguish individuals, based on their location within our unique DNA. Other sources of variation in the genome range from few-base-pair insertions and deletions and short tandem repeats to mega-base-pair variations owing to cytogenetic deletions, insertions, or aneuploidy. Once the human genome was sequenced, it became clear that more than 10% of the genome consists of copy number variations that also generate a unique signature for each individual.[2] The fascinating observation that progression from simple organisms to higher-order organisms and ultimately humans was not associated with a significant increase in the number of genes, but rather, an increasing amount of DNA sequences unassociated with genes, so-called junk DNA. We now know that a substantial portion (≥30%) of this junk DNA is transcribed into noncoding RNA (ncRNA)—RNA that, instead of coding for proteins, serves a direct or indirect regulatory function for those genes that do code for proteins. To date, more than 18 000 distinct ncRNAs have been identified. In many cases, these ncRNAs serve as precursors to generate small inhibitory RNAs, which regulate target gene expression. Other ncRNAs bind proteins and serve as protein translocators and/or

Reprint requests: Rui Zhou, PhD, Departments of Oncology and Biological Chemistry, School of Medicine, Johns Hopkins University, Johns Hopkins All Children's Hospital, St. Petersburg, FL 33701. rzhou13@jhmi.edu.

*Contributed equally.

facilitate the formation of multiprotein complexes. Interestingly, the transcripts of 88% of single nucleotide polymorphisms that have been associated with different phenotypes are actually located within ncRNAs. These single nucleotide polymorphisms could result in different secondary structures, and are thereby likely responsible for differential functions of the ncRNA.

In 2012, the ENCODE project consortium revealed that as much as 80% of the human genome is actively transcribed.[3] However, only about 2% of the genome is protein coding, suggesting the rest of the transcripts are ncRNA transcripts. This discovery led to great interest in unraveling the mechanism governing the biogenesis and function of ncRNAs. Although a vast majority of ncRNAs are transcribed at low levels, and may be transcriptional noise, without any functional role, recent advances of next-generation high-throughput sequencing coupled with functional analyses have yielded numerous discoveries of functional ncRNAs across species.[4,5] The most abundant portion of ncRNAs are housekeeping ribosomal RNAs and transfer RNAs, which are well-known for their functional role in normal cellular processes for quite some time.[4] Recent experiments have primarily focused on ncRNAs other than ribosomal RNAs and transfer RNAs. This minor fraction has been shown to play crucial roles in a myriad of physiologic processes, including genome integrity maintenance, innate immunity, neurodevelopment, and stem cell proliferation and differentiation, as well as diseases such as cancer. These new regulatory noncoding transcripts are traditionally divided into 2 major groups based on their size and an arbitrary cutoff: short noncoding RNAs (18–200 nucleotides) and long ncRNAs (lncRNAs) (>200 nucleotides). In addition, a novel class of ncRNAs was recently discovered, the circular RNAs (circRNAs), named because of the circular nature of the transcript generated from back-splicing of pre-mRNA and covalent linking of 3′ and 5′ ends.[6–9] The size of circRNAs ranges from less than 200 to several thousand nucleotides (Figure 1).

Short ncRNAs are further categorized into several classes, including small nuclear RNAs, which are key components of the spliceosome and play an important role in pre-mRNA splicing, and small nucleolar RNAs, which regulate ribosomal RNA modification. Additional classes of short (21–30 nt) ncRNAs include small interfering RNAs (siRNAs), Piwi-interacting RNAs, and microRNAs (miRNAs or miRs), which are core components of RNA interference (RNAi), an evolutionarily conserved process that regulates gene expression in a sequence-specific manner. The siRNAs are derived from long double-stranded RNA precursors. They join and guide Argonaute protein-containing complexes to target mRNAs by complementary base pairing, leading to gene silencing via RNA degradation. Viral RNA replication intermediates (in the form of double-stranded RNAs) can be converted into siRNAs, which in turn can target viral RNA transcripts for degradation via RNAi.[10–17] Thus, RNAi is a key constituent of antiviral defense mechanism in diverse host organisms. The miRNAs are transcribed as long stem-loop primary transcripts, which are processed into 22- to 24-nt segments.[18–29] Similar to siRNAs, miRNAs are loaded into and guide Argonaute complexes to target mRNAs by imperfect base pairing between miRNAs and target mRNAs, and decrease protein output by mRNA destabilization and translation inhibition.[30–32] Piwi-interacting RNAs are primarily produced in germ cells and control the expression of transposable elements, thereby contributing to the maintenance of germ-line genome integrity.[33]

The lncRNAs are characterized based on location and orientation of resulting transcript into long intergenic ncRNAs, natural antisense transcripts, enhancer RNAs, and bidirectional transcripts.[5,34] LncRNAs are involved in functionally diverse mechanisms. They can serve as transcriptional repressors (eg, *XIST*), enhancers by promoting activating interactions between promoters and distal regulatory elements (eg, *LUNAR1*), miRNAs sponges (eg, *TUG1*), and hubs for protein-protein and protein-nucleic acid interactions (eg, *SPRIGHTLY*).[5,34–39]

The circRNAs are generated by back-splicing reactions during pre-mRNA processing. Emerging evidence has delineated diverse modes of action of circRNAs. For example, the mouse circRNA *CDR1as/CiRS-7* shelters *miR-7* and impacts brain development.[9,40,41] In addition, the circRNA *SRY* plays a prominent role in male sex determination.[9,40] Furthermore, select intron-containing circRNAs can interact with U1 small nuclear ribonucleoprotein particle and promote host gene transcription in the nucleus.[42] Moreover, circRNAs can modulate gene expression by competing with linear splicing.[43] Lastly, selective circRNAs can give rise to functional polypeptides, thereby expanding the complexity of the proteome.[44,45]

Cross-regulation among various classes of RNAs has been well-documented (Figure 2). For example, the lncRNA *TUG1* can sequester and functionally inhibit the activity of a number of miRNAs.[38,46–49] In addition, the lncRNA *H19* serves as a source of precursors for *miR-675* biogenesis.[50–53] An elegant example of ncRNA cross-regulation is the *miR-671-CDR1as-miR-7* axis: the circRNA *CDR1as* carries 1 near perfect binding site for *miR-671* and dozens of imperfect binding sites for *miR-7*. Engagement of *miR-671* with *CDR1as* results in *CDR1as* degradation, which leads to downregulation of *miR-7* owing to loss of protection by *CDR1as*.[9,40,41] Lastly, ncRNAs (lncRNAs and circRNAs) and protein-coding mRNAs can engage with and therefore compete for the same pool of miRNAs, resulting in cross-regulation. In fact, cross-regulation among various mRNAs and between mRNAs and lncRNAs via miRNA engagement provides support for this model.[54]

Functionally, these ncRNAs species regulate cellular identity and function primarily via modulating transcriptional and post-transcriptional gene expression. Given the diverse physiological processes regulated by ncRNAs, it is not surprising that dysregulation of ncRNA expression can contribute to pathological conditions.[55–57] There is now a growing body of evidence implicating ncRNAs in normal development, health, and dysfunctions. We summarize current knowledge on the role of ncRNAs in several diseases and the implications for therapy (Table). We note that extensive literature covering the topic of ncRNAs in pediatric diseases is still developing because the field of is at early stages. In particular, the pediatric translational research applications to date in the rapidly emerging basic science field of ncRNA remain fewer in number than among studies focused on diseases that primarily affect adults. The examples discussed herein are primarily based on studies involving cultured cells or animal models and focus heavily on basic science, and thus may not be specific to children. However, we believe that knowledge gained from these preclinical/early stage clinical studies discussed here will help us to better understand the molecular mechanisms underlying these diseases in the pediatric patient population and facilitate the development of novel diagnostic and therapeutic tools.

Role of ncRNAs in Pediatric Diseases

β-Thalassemia is a recessive inherited disease affecting hundreds of thousands of individuals worldwide, with symptomatic onset in childhood. Before birth, the predominant hemoglobin is $\alpha 2\gamma 2$. In the last trimester, fetal γ globin synthesis decreases and adult β globin synthesis increase. A hallmark of β-thalassemia is a decrease in or absence of β globin synthesis, necessary for the predominant adult hemoglobin ($\alpha 2\beta 2$), resulting in anemia and ineffective erythropoiesis. Current treatments include chelation therapy, blood transfusion, and bone marrow transplantation. Recently, a novel strategy has been explored, which involves reactivation of gene encoding fetal γ globin, to compensate for the shortage of β globin. A suite of miRNAs that functionally inhibit the γ globin gene transcriptional repressors have been identified and validated: *miR-486–3p* and *miR-210* (which target *BCL11A* mRNA), *miR-23a* (against *KLF-2*), *miR-15a* and *miR-16–1* (against *MYB*), and *miR-27a* (against *Sp1*).[58–60] Experimental approaches that enhance the activities of these miRNAs are expected to induce the γ globin gene, thereby harboring potential as a new approach to treating β-thalassemia. The lncRNAs have also been implicated in β-thalassemia.[61,113,114] For example, the nuclear lncRNA *HMI-LNCRNA* generated from the *HBS1L-MYB* enhancer region displays significantly higher levels of expression in erythroblasts derived from cultured adult peripheral blood cells, which express more β globin, compared with erythroblasts from cultured cord blood cells, which express more γ globin. Notably, downregulation of *HMI-LNCRNA* in HUDEP-2 cells, which express mostly β globin, significantly reactivates γ globin expression and promotes erythroid maturation. Thus, *HMI-LNCRNA* might be a potential therapeutic target for γ globin induction treatment in β-thalassemia.

Duchenne muscular dystrophy (DMD) is a lethal neuromuscular disease and is the most common muscular dystrophy affecting children. DMD is characterized by a rapid progression of muscle degeneration caused by mutations in the *dystrophin* gene. Several miRNAs have been implicated in DMD. For example, the muscle-enriched miRNA *miR-486* is markedly decreased in the muscles of dystrophin-deficient mice and in DMD patient samples. Mechanistically, *miR-486* suppresses the expression of phosphatase and tensin homolog (PTEN) and Foxo1a, negative regulators of phosphoinositide-3-kinase (PI3K)/Akt signaling, which regulates muscle hypertrophy and growth, as well as dedicator of cytokinesis 3 (DOCK3), thereby playing a key role in myotube survival.[62,115] In addition, *miR-21* expression is significantly increased in DMD samples, and correlates with a significant reduction in the expression of *miR-21* target transcripts including PTEN and SPRY-1 (Sprouty homolog 1), whereas *miR-29a* and *miR-29c* are significantly decreased in Duchenne muscle and myoblasts, accompanied by a concordant increase in *miR-29* target transcripts, including *COL3A1*, *FBN1*, and *YY1*.[63] Several additional muscle-enriched miRNAs, such as *miR-1*, *miR-133*, and *miR-206* display an increase in the serum of DMD patients and/or in muscle tissues of mouse DMD models, suggesting that they may serve as biomarkers for DMD. When it comes to lncRNAs, it has been shown that the lncRNA *linc-MD1* can operate as a miRNA sponge by sequestering *miR-133* and *miR-135*, thereby modulating the expression of *Maml1*, *Mef2c*, *Myog*, and *Mhc*, which regulate muscle-specific gene expression. In the muscle of DMD patients the level of *linc-MD1*

is greatly reduced, whereas *linc-MD1* overexpression can rescue the defective myogenic differentiation and restore the normal expression of the aforementioned *linc-MD1*-regulated genes.[64] Last, a recent study provided evidence that the circRNA *circ-ZNF609* can be translated into a functional protein that modulates myogenesis, thereby adding circRNAs to the list of regulatory RNAs in muscle development.[44,45]

Rett syndrome is a neurodevelopmental disorder associated with mutations in the *MeCP2* gene encoding methyl-CpG binding protein 2. It has been reported that the MeCP2 protein associates with the miRNA biogenesis machinery and is required for appropriate post-translational processing of a suite of miRNAs.[65] Among these MeCP2-regulated miRNAs is *miR-199a*, which suppresses the expression of inhibitory factors of mammalian target of rapamycin (mTOR) signaling that has been implicated in Rett syndrome. Besides miRNA regulation, MeCP2 can also modulate lncRNA expression. MeCP2 loss in the mouse brain is associated with upregulation of 2 lncRNAs, *AK081227* and *AK087060*.[116] In particular, elevated expression of *AK087060* in MeCP2 knockout mouse brain correlates with an increase in the expression of its host gene *Arhgef26* encoding a Rho guanine nucleotide exchange factor that contributes to axon patterning.[66,67] Thus, it is possible that dysregulation of *AK087060* and *Arhgef26* upon MeCP2 loss in mouse brain contributes to Rett syndrome phenotypes. In contrast, elevated expression of *AK081227* is associated with downregulation of *gamma-aminobutyric acid* (*GABA*) *receptor subunit rho 2* (*Gabrr2*). Because dysfunction in GABAergic inhibitory neurotransmission is associated with many neurodevelopmental disorders, including Rett syndrome, and that the expression of another GABA receptor subunit member (*GABRB3*) is reduced in Rett syndrome, it is likely that *AK081227* and *Gabrr2* are candidates to be altered in Rett syndrome.[69,70,117,118] Lastly, the observation that most circRNAs are enriched in the brain suggests a functional relevance in neurodevelopment. In fact, the circRNA *CDR1as/CiRS-7* plays a key role in brain development, at least in part, by associating with and stabilizing *miR-7*.[9,40,41] We envision that advances in circRNA study will continue to provide insights regarding the role of circRNAs in normal neurodevelopment and neuro-logic diseases, such as Rett syndrome.

Glioma is a cancer originating in glial cells that are primarily involved in nourishment and upkeep of neighboring neurons.[119] Gliomas are the most common brain tumor in children. The most frequent form, low-grade gliomas, are generally not associated with poor prognosis whereas high-grade glioma are often fatal.[120] Various differentially regulated miRNAs and lncRNAs have been identified in gliomas.

Oncogenic miRNAs that promote glioma pathogenesis include *miR-9/9** that regulates *SOX2*, *PTCH1*, *FOXP1*, and *CAMTA1*, the *miR-17–92* cluster targeting *CFTG*, and *miR-17*, *miR-19a/b*, *miR-26a*, and *miR-221/222* that inhibit tumor suppressive PTEN signaling.[71–79] Tumor suppressor miRNAs, such as *let-7a*, *miR-101*, *miR-124*, *miR-138*, *miR-214*, and *miR-708* are involved in inhibiting glioma/glioblastoma growth, particularly by targeting EZH2-dependent epigenetic mechanisms.[80–85] Other tumor suppressor miRNAs in high-grade glioma include *miR-7* (targeting *EGFR*), *miR-128* (targeting *EGFR*, *WEE1*, *MSI1*, and *RPS6KB1*), *miR-34a* (targeting *CDK6* and *CCND1*), and *miRNA-100* (targeting *PLK1*).[86–93]

LncRNAs are also found to be associated with *IDH1/2* mutation status and glioma grade, thereby highlighting their potential diagnostic and prognostic significance.[121] Importantly, select lncRNAs have been analyzed for potential functional role in gliomas. For example, the lncRNA *H19* is upregulated in gliomas where it acts as oncogene by sequestering *miR-140* and *miR-29a*, thereby relieving their inhibitory effect on key oncogenes such as *CDK6*, *CASH2*, *MDR*, and so on.[94,95] Another lncRNA, *HOTAIR*, can activate the fibroblast growth factor (FGF), PI3K/AKT, and MEK pathways and promote glioma proliferation and metastasis by serving as a *miR-326* sponge, and regulate cell cycle progression in glioma via interaction with EZH2.[96,97] Of note, *HOTAIR* has also been shown to be activated by epigenetic regulator BRD4 in glioma genesis, a well-known oncogene across cancer types.[122] In addition, the lncRNA *MEG3* inhibits cell proliferation via p53 activation.[98] Furthermore, the lncRNA *TUG1* maintains glioma stem cells through interactions with PRC2 components (EZH2 and SUZ12) and transcription factor YY1, thereby epigenetically suppressing multiple neuronal differentiation-associated genes.[99] Moreover, the lncRNA *GAS5* suppresses glioma stem cell proliferation, migration, and invasion by binding to the oncogenic *miR-196a-5p* and upregulating the downstream *FOXO1*.[100] Lastly, *XIST* is another oncogenic lncRNA that modulates epigenetic pathways and promotes cell proliferation and migration in gliomas.[123]

Medulloblastoma represents the most common malignant pediatric brain tumor, localized in cerebellum. Recent genetic and epigenetic studies have characterized medulloblastoma into four clinical and molecular subgroups, namely, wingless (WNT), sonic hedgehog (SHH), group 3, and group 4 (reviewed in[124]). As of now, miRNAs and lncRNAs are the predominant ncRNA species that have been investigated in medulloblastoma pathogenesis (reviewed in[101]). Both miRNAs and lncRNAs show subgroup specific expression pattern, thereby highlighting subgroup-specific molecular mechanism regulated by these ncRNA species.

Several miRNA such as *miR-17–92* cluster, *miR-10b* and *miR-21*, have been shown to promote medulloblastoma proliferation and/or metastasis *in vitro* and *in vivo*.[101–104] Conversely, *miR-124*, *miR-218*, *miR-125b*, and *miR-326* are examples of tumor suppressor miRNAs found downregulated in medulloblastomas.[105–110,125,126] Some of these candidates also represent potential therapeutic targets. For example, the *miR-17–92* cluster, which was found to be associated with SHH medulloblastoma, promotes tumor development *in vivo*.[127] Consequently, complete knockout or locked nucleic acid (LNA) based inhibition of the *miR-17–92* cluster reduced tumor growth and improved survival in SHH medulloblastoma mice.

The lncRNAs in medulloblastoma have received comparatively little attention, as of yet. A recent genome-wide lncRNA analysis highlighted subgroup-specific lncRNA expression in medulloblastoma patients and proposed a diagnostic and prognostic model based on lncRNAs.[128] Several other *in vitro* studies also highlight functional role of lncRNAs in medulloblastoma. The lncRNA *MIR100HG* was found to act as oncogene in group 4 tumors where it sponged *miR-19a-3p*, *miR-19b-3p*, and *miR-106a-5p*, thereby derepressing their targets, including *CDK6*, *MYCN*, *SNCAIP*, and *KDM6A*, and promoting proliferation.[111] However, surprisingly, overexpression of *MIR100HG* in the group 3 cell line downregulated

their proliferation. *PVT1* is another oncogenic lncRNA in medulloblastoma, particularly group 3 patients, where it is frequently found fused to oncogene *MYC*.[129] One consequence of the resulting fusion transcript is stabilization of *MYC* mRNA.[112]

CircRNAs are also gaining interest in medulloblastoma research. It has been shown that various cancer types display distinct circRNA signatures and that circRNAs may serve as tumor biomarkers.[130,131] In addition, Lv et al recently identified and validated 33 circRNAs that are dysregulated in medulloblastoma.[132] Interestingly, 2 circRNAs (*circ-SKA3* and *circ-DTL*) seem to modulate expression of corresponding host genes and impact the proliferation, migration, and invasion of tumor cells. Considering that circRNA research is still at infancy, we expect that rapid progress in this field will solidify the notion that circRNAs can modulate and perhaps drive the development and progression of various cancer types, such as medulloblastoma.

Conclusions and Future Directions

We have summarized several physiologic processes regulated by ncRNAs, and provide examples of a wide variety of diseases resulting from ncRNA dysregulation. Although the examples discussed herein may not be strictly specific to children, similar, if not identical, underlying molecular mechanisms operate in both adults and children. We envision that the exciting field of transcriptomics and ncRNA research, which encompasses both basic science and translational studies, will continue to benefit from rapid advances in the development of next generation sequencing technology and bioinformatics tools. This will facilitate the elucidation of the molecular mechanism underlying the function and regulation of ncRNAs in physiological and pathological settings, and provide insights into the development of ncRNA-based diagnostic and therapeutic strategies against pediatric diseases.

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Author Disclosures

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Glossary

circRNA	Circular RNA
DMD	Duchenne muscular dystrophy
GABA	Gamma-aminobutyric acid
lncRNA	Long ncRNA
miRNA	MicroRNAs
ncRNA	Noncoding RNA

SHH	Sonic hedgehog
siRNA	Small interfering RNA

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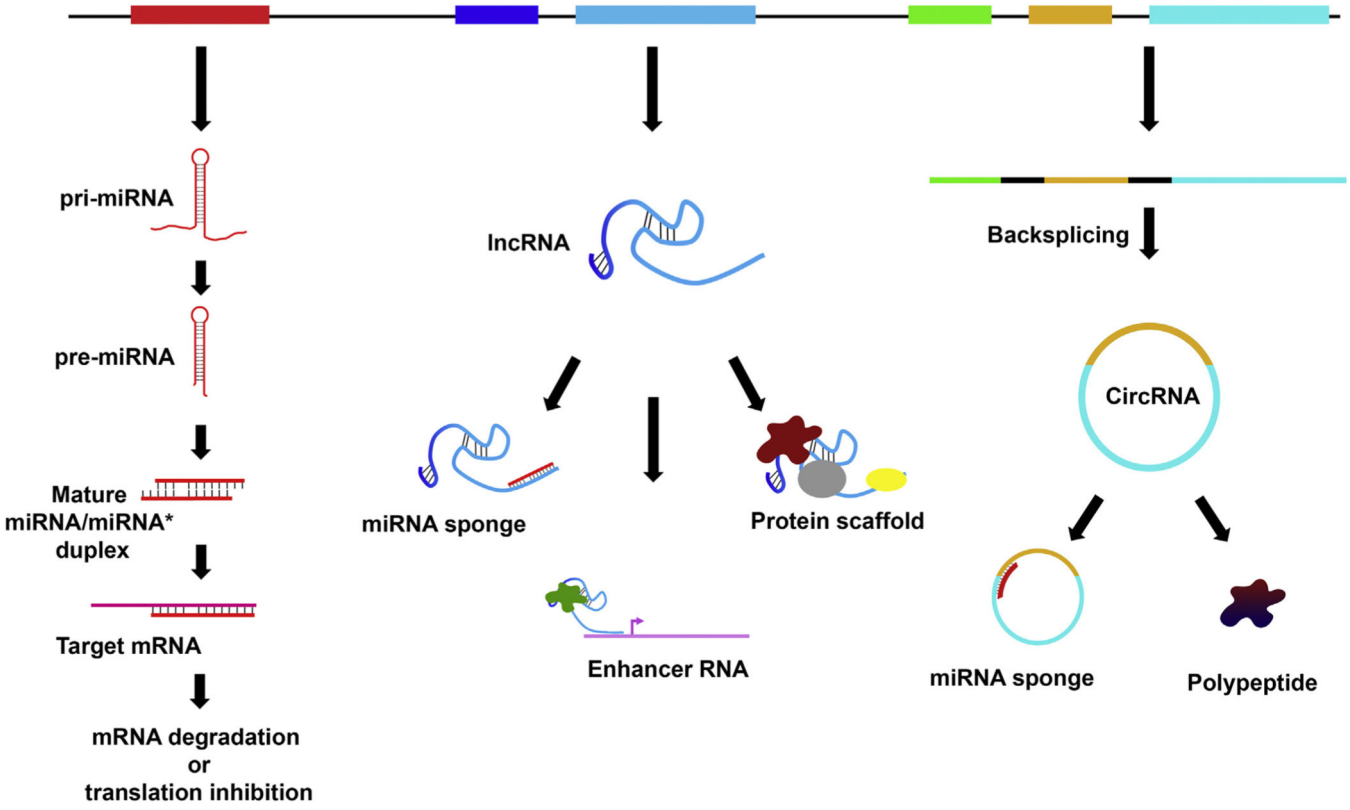

Figure 1.

A schematic illustrating various ncRNAs. The biogenesis mechanisms and functions of various ncRNAs are shown (miRNAs, left; lncRNAs, middle; circRNAs, right). *pri-miRNA*, primary microRNA.

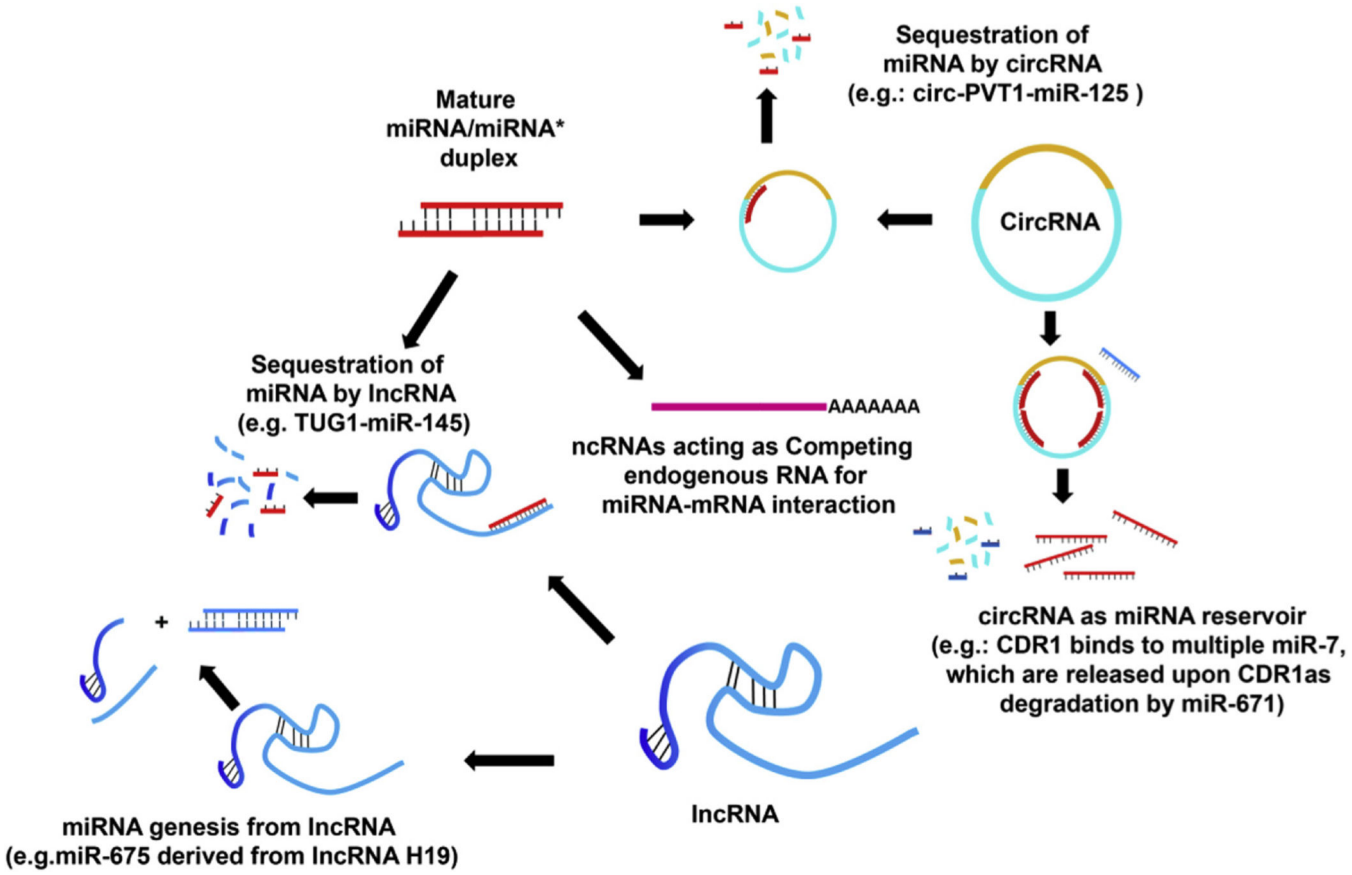

Figure 2.

A schematic depicting cross-regulation among various classes of ncRNAs. On the one hand, miRNAs can bind and downregulate the expression of target lncRNAs; on the other hand, select lncRNAs can serve as miRNA precursors or sequestrate and functionally inhibit miRNAs. In addition, select circRNAs can inhibit or protect miRNAs by physically associating with miRNAs. Conversely, miRNAs that carry perfect complementarity to circRNAs can lead to target circRNA degradation. Last, both lncRNAs and circRNAs can serve as competing endogenous RNAs by sequestrating miRNAs, thereby modulating the availability of miRNAs to engage with and functionally inhibit target mRNAs.

Table.

ncRNAs implicated in various diseases

Diseases	ncRNA	Mechanism	References
β-thalassemia	*miR-486-3p* and *miR-210*	Repressing *BCL11A*	58
	miR-23a	Repressing *KLF-2*	59
	miR-15a and *miR-16-1*	Repressing *MYB*	60
	miR-27a	Repressing *Sp1*	59
	HMI-LNCRNA	Repressing γ-globin	61
DMD	*miR-486*	Repressing *PTEN* and *Foxo1a*	62
	miR-21	Repressing *PTEN* and *SPRY-1*	63
	miR-29a and *miR-29c*	Repressing *COL3A1, FBN1* and *YY1*	63
	linc-MD1	Sequestering *miR-133* and *miR-135*	64
	circ-ZNF609	Encoding a new protein	44,45
Rett syndrome	*miR-199a*	Derepressing mTOR signaling	65
	AK087060	Dysregulation upon MeCP2 loss contributes to Rett syndrome	66-68
	AK081227	Elevated expression correlates with downregulation of *Gabrr2*	68-70
Glioma	*miR-9/9**	Repressing *SOX2, PTCH1, FOXP1* and *CAMTA1*	71-73
	miR-17-92 cluster	repressing *CFTG*	74,75
	miR-17, miR-19a/b, miR-26a and *miR-221/222*	Inhibiting PTEN signaling	76-79
	let-7a, miR-101, miR-124, miR-138, miR-214 and *miR-708*	targeting EZH2-dependent epigenetic mechanisms	80-85
	miR-7	Repressing *EGFR*	86-88
	miR-128	Repressing *EGFR*, WEE1, *MSI1*, and *RPS6KB1*	89-91
	miR-34a	Repressing *CDK6* and *CCND1*	92
	miRNA-100	Repressing *PLK1*	93
	H19	Sequestering *miR-140* and *miR-29a*	94,95
	HOTAIR	Sequestering *miR-326* and interacting with EZH2	96,97
	MEG3	Activating *p53*	98
	TUG1	Interacting with EZH2, SUZ12 and YY1	99
	GAS5	Binding to *miR-196a-5p* and upregulating *FOXO1*	100
Medulloblastoma	*miR-17-92* cluster	Positive effector of Shh-mediated proliferation	101,102

Diseases	ncRNA	Mechanism	References
	miR-10b	Expression positively correlated with *BCL2* expression	101,103
	miR-21	Repressing *PDCD4*	101,104
	miR-124	Repressing *CDK6* and *SCL16A1*	105,106
	miR-218	Repressing *NANOG RICTOR, CTSB* and *CDK6*	107,108
	miR-125b	Repressing *SMO* and *LIFRα*	109,110
	miR-326	Repressing *SMO*	109
	MIR100HG	Sequestering *miR-19a-3p, miR-19b-3p* and *miR-106a-5p* and derepressing *CDK6, MYCN, SNCAIP* and *KDM6A*	111
	PVT1	Stabilizing *MYC*	112

mTOR, mammalian target of rapamycin; *PTEN*, phosphatase and tensin homolog.