Regulatory RNAs and control of epigenetic mechanisms: expectations for cognition and cognitive dysfunction

The diverse functions of noncoding RNAs (ncRNAs) can influence virtually every aspect of the transcriptional process including epigenetic regulation of genes. In the CNS, regulatory RNA networks and epigenetic mechanisms have broad relevance to gene transcription changes involved in long-term memory formation and cognition. Thus, it is becoming increasingly clear that multiple classes of ncRNAs impact neuronal development, neuroplasticity, and cognition. Currently, a large gap exists in our knowledge of how ncRNAs facilitate epigenetic processes, and how this phenomenon affects cognitive function. In this review, we discuss recent findings highlighting a provocative role for ncRNAs including lncRNAs and piRNAs in the control of epigenetic mechanisms involved in cognitive function. Furthermore, we discuss the putative roles for these ncRNAs in cognitive disorders such as schizophrenia and Alzheimer's disease.

Keywords: chromatin • epigenetics • long noncoding RNA • neuroplasticity • neuroscience • short noncoding RNA

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Epigenetic mechanisms have emerged as critical components of the memory formation process and are involved in cognition and cognitive disorders. As related to the nervous system, the term epigenetics refers to long-term, potentially heritable changes in gene expression patterns that do not result from mutations in the DNA sequence. This broad definition encompasses a number of chemical modifications to DNA residues as well as alterations to closely associated molecules such as histone proteins or chromatin-associated RNAs [1]. These epigenetic modifications (also referred to as epigenetic marks) are involved in numerous cellular and molecular functions, ultimately influencing nuclear organization and transcriptional activity at chromatin regions [1]. The semipermanent nature of these epigenetic modifications thus allows genetically identical cells to differentiate into distinct lineages, express unique gene patterns, and perform unique functions in a lineage-dependent fashion [2,3].

As the epigenome plays an important role in driving cellular development, it is not sur-

prising that epigenetic mechanisms critically control the development of the nervous system [4–7]. However, in the past decade it has become increasingly clear that despite the postmitotic state of most neurons, epigenetic mechanisms continue to play a critical role in controlling transcription into adulthood (reviewed in [8]). This is especially evident in the context of transcription-dependent cognitive processes such as long-term memory formation, where altered epigenetic processes can either impair or improve performance in memory tasks.

While the importance of epigenetic regulation in cognition has been well established, the mechanisms by which epigenetic marks are targeted to particular genes or loci remain relatively unexplored. Instead, most studies to date have examined either global changes in the levels of epigenetic marks within specific brain regions or the presence of epigenetic marks at particular genes and promoters with known cognitive function. As a result of these studies, it is becoming increasingly clear that the neuro-epigenetics

landscape can differ significantly within and across brain regions, and that dysregulation of chromatin-modifying enzymes (CMEs) can have profound effects on brain function, and thereby, cognition and cognitive disorders [9–11]. Indeed, evidence suggests that dysfunction of epigenetic processes is involved in the etiology of many cognitive disorders, including schizophrenia, bipolar disorder and major depressive disorder [9]. Such studies have advanced our knowledge of the role of epigenetic mechanisms in specific brain regions, and have given rise to the rapidly expanding field of cognitive epigenetics. However, as very few CMEs have demonstrated sequence-specific DNA binding, the question of how CMEs are directed to their target gene regions remains largely unsolved. Some observations have indicated that DNA binding proteins, such as the transcription factors including nuclear factor- κ B, Nanog, and Oct4, interact with CMEs to direct site-specific epigenetic gene regulation [12–14]. Additionally, recent studies suggest that multiple families of regulatory RNAs also mediate epigenetic targeting.

To date, a majority of the research studies have described regulatory RNAs with little to no protein-coding potential, thus defined as noncoding RNAs (ncRNAs). Although poorly described relative to protein-coding genes, ncRNAs comprise a major portion of the mammalian transcriptome [15]. While estimates differ as to the abundance of ncRNAs, the general consensus of the field is that ncRNAs are quite plentiful, particularly in brain tissues [15–19]. It remains plausible that regulatory RNAs have both translation-independent functions and protein-coding potential, and indeed, translation-independent activity of mRNAs has been identified in well-studied pathways such as p53 signaling [20–22]. However, the field of epigenetics has largely focused on characterizing such functions in ncRNAs, in part as a precaution against experimental confounds.

Common practice in the epigenetics field describes ncRNAs as either long or short, with the division being set at a length of 200 nucleotides. While seemingly arbitrary, this division allows for the useful separation of the many characterized classes of small functional RNAs, including miRNAs, piRNAs (PIWI-interacting RNAs), siRNAs (small interfering RNA), snoRNAs (small nucleolar RNAs) and tRNAs (transfer RNAs) from the less well characterized long noncoding RNAs (lncRNAs) [23]. Among other functions, both short and lncRNAs have attributable roles in neuronal epigenetic mechanisms [24,25] – a finding with exciting implications for cognitive sciences. In this review, we will highlight key findings that are beginning to elucidate a role for ncRNAs in the control of neuro-

nal and cognitive function via epigenetic mechanisms. Our goal for this review is to draw attention to this phenomenon and encourage new investigations into ncRNA-mediated control of the epigenome in cognition and cognitive disorders. Further, while miRNAs are well studied with regard to cognitive disorders, they are poorly studied in the context of epigenetic function. In contrast, while piRNAs and lncRNAs are better characterized in the context of epigenetic function, they are poorly studied with regard to cognitive disorders – even though many such disorders involve dysregulation of the epigenome. Nonetheless, emerging studies are beginning to explore the interesting idea that ncRNAs are involved in the epigenetic process underlying cognition and may be altered in cognitive disorders.

Short ncRNA

Mechanisms of canonical RNA interference

When Lee and colleagues [26] first demonstrated that the small (22-nucleotide) ncRNA dubbed lin-4 represses the translation of several developmental genes in *Caenorhabditis elegans*, the scientific community failed to recognize this discovery as anything more than a curious feature of the invertebrate model's genetics. As a consequence, few of these ncRNAs were identified or characterized until the discovery of RNA interference (RNAi), a post-transcriptional regulatory process that will be reviewed and discussed in later sections. However, we begin our discussion with small regulatory RNAs initially shown to be highly conserved in plants and animals in the early 2000s [27]. Today, the known roles of miRNAs and their related structures have expanded to encompass the view that as many as 60% of protein-coding RNAs are regulated by miRNA activity [28,29]. Since the days of Ambrose and Lee, tens of thousands of miRNAs have been annotated [30–34], and miRNAs have been shown to regulate such diverse biological processes as developmental pattern formation [27], pluripotency [35], cell signaling [36], cardiovascular disease [37], cancer [38], diabetes [39], neural plasticity and memory [40], among others [41]. This review will largely describe miRNAs as they relate to the epigenome; however, in order to better understand how miRNAs have come to be associated with epigenetic activity, it is first necessary to understand the canonical post-transcriptional pathway by which these miRNAs regulate gene expression.

In the canonical pathway (reviewed in [42]), the nascent miRNA begins as a transcript of intronic or intergenic DNA, a miRNA precursor molecule known as a primary miRNA (pri-miRNA). While still in the nucleus, this pri-miRNA is bound and cleaved by a microprocessor complex composed of Drosha and

Dgcr8. Processing of the pri-miRNA by this complex leads to the formation of a shorter hairpin-like structure defined as a precursor miRNA (pre-miRNA) [42,43]. The pre-miRNA is then exported into the cytoplasm via Exportin 5 where it undergoes further cleavage by the RNAase enzyme *Dicer*, thereby forming a complementary duplex of two miRNA strands. Unwinding of this duplex releases one of the RNA strands, while the remaining strand is bound to an AGO protein in the RNA-induced silencing complex (RISC). The mature miRNA, coupled with RISC (now referred to as miRISC), then functions to detect complementary sequences inside messenger RNAs, usually found in the 3'-untranslated region of the target mRNA [43,44]. The binding of this miRISC complex to a target mRNA results in silencing of the mRNA, which may occur either by degrading the target transcript via the endonuclease activity of AGO2, or by simply preventing translation of the target transcript in cases of less perfect complementarity.

Although studies have generally focused on the regulation of mRNA by the canonical RNAi pathway, there is considerable evidence that interaction between canonical RNAi and other ncRNA signaling pathways occurs and may have broad ramifications in neuroplasticity and cognition (reviewed in [45]). Many miRNAs are expressed in the brain, and a number of studies have examined their role in cognitive disorders (Table 1) [46]. Indeed, roles for miRNA have been attributed to molecular signaling in neurodevelopment [47], neural stem cell differentiation [48,49] and cortical neurodegeneration [50,51], where knockout of the enzyme *Dicer* results in the dysregulation of these processes. Intriguingly, studies using an inducible *Dicer1* knockout mouse model demonstrate improved performance in several memory tasks, suggesting that miRNA signaling may also act to restrict memory formation in some cases [52].

Canonical miRNA signaling in schizophrenia

Among miRNA-related cognitive disorders, schizophrenia is perhaps the most extensively studied. Patients suffering from DiGeorge Syndrome often experience microdeletions affecting the miRNA microprocessing gene *Dgcr8*, and are 30-times more likely to suffer from schizophrenia or schizoaffective disorders [66]. This observation suggests a critical importance for miRNA signaling in schizophrenia. Postmortem studies in the brains of schizophrenic patients have identified dysregulation of two miRNAs, miR-132 and miR-219, both of which have been linked to schizophrenia-associated cognitive or behavioral impairments [60,67–69]. Both miRNAs are dysregulated in response to NMDA-receptor blockade [42], an inter-

esting finding in light of the hypothesis that hypofunction/downregulation of the NMDA receptor plays a critical role in schizophrenia pathophysiology. A third candidate, miR-195, is increased in the brains of patients with schizophrenia, where it regulates several schizophrenia-related genes, including *Bdnf* [70], *Reln*, *Vsnl1*, *Htr2a* and *Grin3* [71]. Indeed, *in silico* studies of miRNAs associated with transcription factors suggest that miR-195 plays a central role within a regulatory network of schizophrenia-related genes [63].

Because schizophrenia is a heterogeneous and complex disorder that involves several brain regions and cell types, the role miRNAs in the control of gene transcription must be considered in this context as well. For example, patients with schizophrenia are known to exhibit a wide range of up-regulated miRNAs in the superior temporal gyrus and prefrontal cortex, including miR-107, miR-15a, miR-15b, miR-16, miR-195, miR181b, let-7e, miR-20a, miR-26b, miR-19a [71]. Interestingly, none of the miRNAs described above are specific to neurons: miR-219 regulates oligodendrocyte maturation [72], while miR-195 and miR-132 are expressed in astrocytes [73–75]. Comprehensive studies should further elucidate the role of miRNAs in the nervous system, as well as test the possibility that global changes in miRNA processing may result in the disease's pathogenesis [71].

While the miRNAs described above target schizophrenia related genes directly, there is also evidence for miRNA-mediated epigenetic dysfunction in schizophrenia, and some schizophrenia-related miRNAs are known to be more directly involved in epigenetic regulation via the targeting of CMEs (Figure 1). Such regulatory miRNAs include miR-132, miR-212 and miR-195 [64,71,76–77]. miR-132, which was described above, is downregulated in the prefrontal cortex (PFC) of patients with schizophrenia, and regulates expression of DNA methyltransferase 3 α (DNMT3- α), thereby regulating DNA methylation [60]. This is especially interesting, considering that DNMT3- α is known to be upregulated some brain regions in schizophrenia – including the PFC (see [78] for review). Another promising candidate is miR-137, an miRNA identified as having a SNP strongly associated with schizophrenia in a meta-analysis of genome-wide association studies [79]. miR-137 targets multiple chromatin-modifying genes [80], including the histone-lysine *N*-methyltransferase *EZH2* [81], as well as the lysine-specific histone demethylase 1A (*KDM1A*), which governs neuron differentiation and migration [62]. While such epigenetic regulation may occur, future studies are required to determine the exact nature and extent of miRNA-mediated epigenetic regulation in

Table 1 Examples of noncoding RNAs in epigenetically-linked cognitive disorders.

Name	Type	Putative epigenetic MOA	Disorder	Ref.
17A	lncRNA	None indicated	AD	[53]
1810014B01Rik	lncRNA	None indicated	AD, PD	[53]
BACE1-AS	lncRNA	None indicated	AD	[54]
GDNFOS	lncRNA	None indicated	AD	[53]
Gomafu	lncRNA	Binds to the polycomb repressor complex, PRC1	Scz, Anx	[55]
Malat-1	lncRNA	Associates with the EZH2 subunit of the polycomb repressor complex	Alc	[56]
NAT-Rad18	lncRNA	None indicated	AD	[53]
Sox2OT	lncRNA	None indicated	AD, PD	[57]
miR-106b	miRNA	None indicated	Scz	[58]
miR-125a	miRNA	–	MDD	[59]
miR-132	miRNA	Targets the DNA methyltransferase DNMT3- α	Scz, MDD	[60,61]
miR-137	miRNA	Targets the EZH2 subunit of the polycomb repressor complex; targets the histone demethylase KDM1A	Scz	[62]
miR-16	miRNA	None indicated	Scz	[58]
miR-182	miRNA	None indicated	MDD	[59,61]
miR-195	miRNA	None indicated	Scz	[63]
miR-212	miRNA	None indicated	Scz	[64]
miR-219-3p	miRNA	None indicated	Scz	[58]
miR-298	miRNA	None indicated	MDD	[59]
miR-29c	miRNA	None indicated	AD	[65]

AD: Alzheimers disease; Alc: Alcoholism; Anx: Anxiety; MDD: Major depressive disorder; MOA: Mechanism of Action; PD: Parkinsons disease; Scz: Schizophrenia.

the development and pathophysiology of cognitive disorders such as schizophrenia.

Canonical function of siRNA-mediated RNA interference

There are significant functional similarities between miRNA- and siRNA-mediated RNAi. In this section we will highlight some of the more unique aspects of siRNA generation and regulation. Similar to miRNAs, siRNAs are short (~21 nucleotide), noncoding transcripts that are canonically generated from exogenous dsRNAs. When siRNAs were first discovered in plants by David Baulcombe and colleagues [82], they appeared to function as part of a natural, antiviral immune response. Upon exposure, exogenous, double-stranded RNAs (dsRNAs) – often from viruses – are digested by Dicer in the cytoplasm, generating short RNA duplexes. These RNA duplexes are bound by AGO as part of the RISC complex and guide the complex to a complementary target, in this case, a copy of the viral RNA. Once bound, the endonuclease ‘slicer’ activity of AGO2 is further activated by

the complementation of the siRNA-target interaction, thus mediating target destruction [83]. In this fashion, canonical siRNA-mediated RNAi initiation turns viral RNA against itself for destruction. Interestingly, newly discovered noncanonical mechanisms of endogenous siRNA (endo-siRNA) generation and function are gaining increased relevance in cognitive neuroscience. Below, we discuss emerging roles for siRNA-directed epigenetic regulation of gene expression changes.

Emerging mechanisms of siRNA directed epigenetic regulation

siRNAs participate in epigenetic regulation of genes through DNA methylation as well as by histone modification (Figure 2) [84,85]. The precise mechanism of siRNA generation depends on the organism involved. In *Schizosaccharomyces pombe*, endo-siRNAs are generated by an RNA-directed RNA polymerase complex (RDRC), and epigenetic regulation is carried out by the RNA-induced transcriptional silencing (RITS) complex, with the latter being dependent on siRNAs gener-

ated by the former (for review see [86]). In *Arabidopsis thaliana*, this process involves two plant-specific RNA polymerase II related RNA polymerase enzymes: Pol IV and Pol V [87]. First, transcripts from Pol IV are used as templates by the RNA-dependent RNA polymerase RDR2 to form dsRNA which is reduced into 24-nucleotide duplexes by the *Dicer* protein DCL3. From the cytoplasm, one strand of a duplex is then loaded onto AGO4, which translocate into the nucleus [88] and binds to complementary, nascent transcripts created by Pol V [89,90]. Once stabilized to a target transcript by Pol V and the Pol V transcript binding protein KTF1, AGO4 associates with the DRM2 DNA methyltransferase, a writer of the 5 mC epigenetic mark at CHH sites [91]. RDM1, a subunit of the final complex responsible for linking AGO4 to Pol V and DRM2, has itself an affinity for methylated DNA, a finding that suggests a pre-dilection of the Pol V-AGO4 complex for pre-existing sites of methylated DNA. While still speculative, these studies suggest a parallel between siRNA-directed histone modification and siRNA-directed DNA methylation insofar as both may be mediated as part of a self-perpetuating feedback loop [92].

Although endo-siRNA generation and epigenetic function is well-characterized in *S. pombe* and *A. thaliana*, other studies speculate on a potential role in endogenous production of siRNAs and their epigenetic function in human cells [96,97]. Mammalian endo-siRNAs are known to be generated from hybridized mRNAs and antisense transcripts [97], which may then regulate the epigenome. An alternative pathway for the generation of such endo-siRNAs has also been identified in which a complex composed of human TERT (hTERT), Brahma-related gene 1 (*BRG1*) and nucleostemin (NS) – together referred to as the TBN complex-produces dsRNAs. These dsRNAs can then be processed into siRNAs that facilitate the formation of heterochromatic regions [98].

Promisingly, several studies demonstrate endo-siRNA-mediated histone methylation and DNA methylation in cultured mammalian cells [84–85,99]. The mechanistic actions of mammalian endo-siRNA are poorly characterized; moreover, a neurological role for these endo-siRNAs also remains to be established, as little neuroepigenetic research has focused on these mechanisms. Importantly, targeted sequencing studies

Figure 1. Canonical mechanism of miRNA generation and epigenetic regulation. (A) Schematic of canonical miRNA biogenesis. Pri-miRNA are transcribed by RNA Pol II, and stem-loop regions are processed by Drosha and DGCR8. The resulting pre-miRNA is exported through the nuclear membrane into the cytoplasm, where Dicer further cleaves the pre-miRNA into a short double-stranded RNA region. A guide strand is selected and bound by AGO within the RISC complex, while the passenger strand is cleaved and degraded. **(B)** miRNA and siRNA in conjunction with the cytoplasmic RISC complex target proteins involved in epigenetic regulation at the mRNA level. This post-transcriptional silencing, ultimately results in global alterations in the epigenome and cellular function. AGO: Argonaute; CME: Chromatin-modifying enzyme; miRISC: miRNA in complex with RISC; PTM: Post-translational modifications; Pri-miRNA: Primary miRNA; Pre-miRNA: Precursor miRNA; RISC: RNA-induced silencing complex.

Figure 2. Epigenetic regulation by nuclear short noncoding RNA. Proposed mechanisms of sncRNA-mediated epigenetic regulation. **(A)** Studies have demonstrated short non-coding RNA (sncRNA)-mediated targeting of mRNA cotranscriptionally. This results in the recruitment of AGO or PIWI proteins to the gene locus of nascent transcripts and may result in the recruitment of CMEs and epigenetic regulation via DNA methylation or the post-translational modification of associated proteins, such as histones [93,94]. **(B)** sncRNAs in complex with AGO/PIWI also associate directly with DNA. This results in the recruitment of CMEs and epigenetic regulation [95]. AGO/PIWI indicates a member of either the argonaute or PIWI family of proteins. CME: Chromatin-modifying enzyme; DNMT: DNA methyltransferase; PTM: Post-translational modifications; RNA Pol II: RNA polymerase II.

demonstrate a large number of these RNAs in human somatic cells [100], and recent studies have identified putative endo-siRNA populations in hippocampal tissues [101,102]. Thus, indicating a potential epigenetic role for endo-siRNAs in neuronal alterations.

piRNAs: regulators of the epigenome and neuroplasticity

In exploring the role for ncRNAs in cognition and cognitive sciences, piRNAs have become a topic of some intriguing investigations. piRNAs are distinguished from siRNAs by their size (they are slightly longer at 26–31 nt rather than 20–24 nt), and association with PIWI proteins, a clade of the AGO family [103]. Unlike miRNAs and siRNAs, piRNAs are generated from single-stranded RNA species in a *Dicer*-independent manner [104]. piRNAs are preeminently expressed and

best characterized in the context of germ cell development [105–107]. Indeed, the name ‘PIWI’ has its humorous origin owing to the discovery of the ‘P-element induced wimpy testis’ in the gonadal cells of *Drosophila*. PIWI proteins translocate into the nucleus in an RNA-dependent manner, guided by piRNAs [107,108] where they serve to silence transposons in the nuclei of germ cells [109], ostensibly for the purpose of genome protection in the vulnerable germline DNA. However, this functionality is not exclusive, as protein-coding genes may also code for piRNAs [110]. Moreover, recent studies provide evidence for numerous piRNAs expressed in adult organ tissues, including in the brain, suggesting new possibilities for epigenome regulation in neurons [111,112].

With regard to epigenetic initiation and targeting, piRNAs have been shown to target heterochromatic

regions with the help of bound heterochromatin protein 1a (HP1a) as part of a PIWI-piRNA complex [113]. This complex typically associates with repressive histone lysine methylation marks, but may also facilitate transcription [114], and some evidence suggests that piRNA could form an initiator complex on chromatin that recruits other chromatin-modifying agents [115]. Additionally, Carmell and colleagues provide an interesting set of studies that suggests chromatin regulation by piRNAs. Specifically, Carmell and colleagues demonstrate that knockout of a murine PIWI results in increased transposon expression due to a loss of inhibitory DNA methylation at transposon sites [116]. Further elucidation of this mechanism by Aravin and colleagues revealed that piRNA-mediated silencing of transposons by PIWI orthologs plays a significant role in maintaining the genome integrity of the mouse testis [117,118]. Interestingly, some transposable elements have been identified as sources of dsRNAs, which feed into the endo-siRNA pathway, suggesting a degree of redundancy between endo-siRNA and piRNA pathways [104]. While still largely unexplored in mammalian systems, at least one population of piRNAs has been identified in the murine hippocampus via next-generation sequencing [119].

With regard to the neuroepigenetic function of piRNAs, recent studies suggest an epigenetically-active population of serotonin-induced piRNAs in the CNS of *Aplysia*. These studies demonstrate (via knockout of PIWI) the necessity of PIWI for serotonin induced long-term facilitation [111] – a synaptic correlate for memory formation. piRNAs have also been demonstrated to silence CREB2 – a suppressor of memory formation – in an activity-dependent manner in *Aplysia* [111], further supporting the idea that piRNA signaling is necessary for memory formation. Collectively, these results are suggestive of a broader role for piRNAs in epigenetic regulation than was previously expected and future studies will likely uncover additional piRNAs mediating neuroepigenetic regulation.

lncRNA

Discovery & characterization of lncRNAs

Typically, sncRNAs can be separated into distinct classes by clearly defined homologies of structure and function, while lncRNAs represent a heterogeneous and often modular set of transcripts [120–122]. As a result, the most common working nomenclature of lncRNA structure describes transcripts on the basis of their genomic location relative to nearby protein-coding genes [23,120]. Among these subcategories of lncRNAs are antisense, bidirectional, intergenic, intronic and overlapping transcripts (Figure 3).

Although the first functional role attributed to a lncRNA was described prior to the discovery of sncRNAs [123], it is only recently that the abundance of lncRNAs in the mammalian transcriptome has been fully recognized. Recent studies have identified thousands of lncRNA genes in the human transcriptome [19,124]. While these studies have expanded our knowledge of the transcriptome, most observations are still limited in scope to cultured cells and resting state expression profiles within tissues. Given the highly specific expression profiles of many known lncRNAs and their comparatively lower expression levels (ten-fold lower than protein coding genes, on average) [125,126], it is likely that many functional lncRNA transcripts are expressed below the power of detection for such studies. Indeed, novel deep-sequencing methodologies

Figure 3. Origins of long noncoding RNAs.

(A–E) Many lncRNA genomic loci are colocalized with protein coding genes, and they are often described in relation to these genes. A number of common naming conventions have come into general use to describe the various protein coding gene associated lncRNAs. (A) Antisense transcripts overlap protein coding genes, but are transcribed from the antisense strand.

(B) Bidirectional transcripts share transcription start sites with protein coding genes, but are transcribed in the opposite direction. (C) Intergenic transcripts do not overlap with protein coding genes. (D) Overlapping transcripts overlap significantly with or encompass protein coding genes on the sense strand. (E) Intronic transcripts are located within a sense-strand intron of a protein coding gene. Solid bars indicate exons of mRNAs (blue), lncRNAs (red). Diagonal stripes indicate overlapping exons. Chevron arrows indicate introns of mRNAs (blue), lncRNAs (red) or overlapping transcripts (alternating red and blue). Curved arrows indicate transcription start sites.

demonstrate that the full transcriptome is much larger than current sequencing studies have revealed [127–129]. A thorough investigation of lncRNA abundance will likely require the targeted transcriptional profiling of specific tissues, cell types or perturbations. Moreover, as many as 80% of mammalian protein coding loci express some form of antisense transcript along with their respective mRNAs [130–132]. Antisense transcripts can often impact the regulation of associated protein coding genes [133], though this is not a necessity, nor does it preclude additional *in trans* effects [23].

In addition to shared genomic loci, lncRNAs and mRNAs share characteristics that distinguish them from other small RNA species. Similar to mRNAs, lncRNAs demonstrate properties such as chromatin structure typical of RNA polymerase II (Pol II) transcription, alternative splicing sites and regulation by transcription factors [134]. Furthermore, many lncRNAs are polyadenylated and capped with 5'-methylguanine [124]. There have even been reports of lncRNAs associating with ribosomes – although ribosome profiling experiments suggest that such associations are usually inactive [135,136]. Surprisingly, some translation of lncRNAs has been observed, resulting in the expression of small protein products, though recent studies suggest that global translation of all ncRNAs may occur in a manner resembling pervasive gene transcription [137], though the importance of this mechanism remains to be defined in any cell system.

lncRNAs impact cellular processes via a number of molecular mechanisms. These include regulation of transcription [138–140], epigenetic regulation [141], scaffolding of protein complexes [142,143], guiding of regulatory complexes [143], acting as decoys to regulatory complexes [144] or simply being transcribed [145]. These mechanisms of action often rely on the ability of RNAs to bind both proteins and nucleic acids in a targeted manner. An RNA molecule's primary structure – that is, the linear sequence of nucleotides – allows RNA transcripts to bind homologous DNA regions via canonical or noncanonical base pairing. Recently, tools have been developed for the computational prediction of lncRNA DNA-binding motifs and binding sites [146]. Similar hybridization also allows single stranded RNA to fold into complex secondary and tertiary structures, and to bind with other RNA molecules. It is these structural arrangements, in addition to sequence specificity, that often underlie interactions with RNA-binding proteins (RBPs) [147,148]. Many currently known mechanisms of lncRNA activity rely largely on interaction with RBPs and alterations in localization, activity or association with other proteins. RBPs are a functionally and structurally diverse class of molecules, and

recent studies have estimated that 40% of RBPs (out of a cohort of 1542 RBPs) are involved in ncRNA-related processes [149]. Additionally, lncRNAs have been observed to bind and regulate other small RNA molecules such as miRNAs [150,151], and extensive noncoding interactomes have been proposed [152].

In the nucleus, lncRNAs modulate gene expression via regulation of transcription and the epigenetic landscape (Figure 4) [134,153]. Indeed, lncRNAs can bind to a number of CMEs, usually 'writers' of epigenetic marks [153]. The extent of such a phenomenon was established in 2009, when it was shown that some 20% of lncRNAs (out of a cohort of 3300) associate with the PRC2, a histone methyltransferase that catalyzes the addition of repressive H3K27 methylation [154]. Additionally, binding of lncRNAs to CMEs can prevent or restrict CME activity, as was recently demonstrated to occur at the CEBPA locus, where an overlapping lncRNA (sometimes described as an extracoding RNA or ecRNA) preferentially binds the DNA methyltransferase DNMT1 [144], ultimately leading to decreased local DNA methylation. Interestingly, this phenomenon is not restricted to the CEBPA locus but occurs at multiple methylation sites across the epigenome [144].

lncRNAs in cognitive disorders

The importance of epigenetics is becoming increasingly recognized in neuronal alterations and cognitive function. A recent GWAS study of common cognitive disorders found that epigenetic – specifically, histone methylation – pathways were strongly associated with impaired cognition [9], and a number of screening studies suggest that lncRNA dysregulation is associated with neurodevelopmental and cognitive disorders [155], including Rett syndrome [156], autism [157] and Fragile X syndrome [55]. While the widespread mechanisms of ncRNA-mediated regulation have been established for some time, only in very recent years have these mechanisms been investigated in a neurological or cognitive context. lncRNAs have been found to be co-expressed with genes that are critical for neuronal activity, including *C-fos*, *Arc* and *BDNF*, suggesting an extensive network of protein coding and noncoding genes involved in neuronal plasticity [55,158]. Additionally, lncRNAs are known to play a role in normal brain development [159]. While the majority of lncRNA transcripts have been characterized either in cell culture or during development, efforts to examine the functional roles of neuronal lncRNAs in cognition are still continuing. Here, we will recount some of the better-characterized examples of lncRNA functioning in the context of the adult brain, and their impact on cognition or cognitive disorders.

Figure 4. IncRNA-mediated epigenetic regulation. IncRNAs possess a number of mechanisms by which they initiate or facilitate epigenetic regulation, and multiple archetypal functions are often utilized within a single IncRNA transcript. **(A)** IncRNAs often recruit chromatin-modifying enzymes in *cis*, thereby mediating epigenetic regulation of nearby genes (dimitrova, zhang, redrup). **(B)** IncRNAs may also act as guides, targeting associated CMEs to target loci in *trans*, potentially through direct interaction with target regions. **(C)** IncRNAs may act as scaffolding factors, and mediate the assembly of ribonucleoprotein complexes with multiple regulatory functions. This may occur either in *cis*, as occurs with the direct CMEs to target loci in *trans*. CME: Chromatin-modifying enzyme; DNMT: DNA methyltransferase; PTM: Post-translational modifications; RNA Pol II: RNA polymerase II; RNP complex: Ribonucleoprotein complex.

Malat1

One IncRNA that has been observed to regulate neuronal activity is Malat1 (also known as Neat2). This highly conserved nuclear IncRNA is expressed in numerous tissues, with a high degree of expression in neurons [160]. Knockdown studies of Malat1 have resulted in decreased synaptic density in cultured hip-

pocampal neurons [160], and postmortem studies have demonstrated that Malat1 is upregulated in multiple brain regions in both human alcoholism as well as rodent models of alcoholism [56]. Malat1 can regulate gene expression *in cis*, thus controlling the expression of proximally located genes which are involved in nuclear function [138]. Conversely, Malat1 can associate with

hundreds of sites *in trans*, where it preferentially binds the gene body of active genes in a transcription-dependent fashion [161]. Epigenetically, Malat1 has been shown to associate *in vivo* with EZH2, a subunit of the PRC2 [162]. Interestingly, and despite many functional associations, Malat1 knockout in mice does not affect viability or normal development [138,163].

Gomafu

The lncRNA Gomafu has also been shown to play multiple roles in the adult brain. Gomafu has been observed to govern SZ-related alternative splicing by acting as a splicing factor scaffold for QK1 and SRSF1, and it is known to be dysregulated in postmortem studies of schizophrenia patients [164]. Recently, an additional study has suggested that Gomafu functions *in cis* to mediate epigenetic regulation of gene expression via the PRC1 complex, and that knockdown of Gomafu in adult mice results in abnormal behavioral phenotypes and increased anxiety [55].

BACE1-AS

Another example of lncRNAs involved in neuronal disorders, is the antisense lncRNA, BACE1-AS that has been implicated in Alzheimer's disease (AD). AD is a progressive neuro-degenerative disorder which has been previously associated with epigenetic dysregulation, particularly in histone acetylation [165,166]. A characteristic marker of AD pathology is the accumulation of β amyloid plaques consisting of oligomerized amyloid β peptides. These plaques form as a result of the processing of amyloid precursor proteins (APP), the rate limiting step of which is the cleavage of APP by the Beta-secretase enzyme (BACE1) [167]. Dysregulation of BACE1 contributes to AD pathology via the overproduction of A β [167]. Recent studies have identified an antisense lncRNA at the BACE1 locus (BACE1-AS) which physically associates with and stabilizes BACE1 mRNA, increasing BACE1 expression both *in vitro* and *in vivo*, and ultimately resulting in increased generation of A β [54]. BACE1 mRNA is targeted by the miR-485-5p, which normally results in BACE1 repression; however, BACE1-AS prevents this repression by competitively binding the miRNA target site [168]. Both the BACE1-AS lncRNA and BACE1 mRNA are overexpressed in the parietal lobe and in the cerebellum of postmortem AD patients, suggesting a relevant mechanistic link between the BACE1-AS lncRNA and the pathophysiology of AD [168]. Interestingly, knockdown of BACE1 or BACE1-AS results in reduction of Alzheimer's pathology in an APP mouse model of AD [169].

While the dysregulation of lncRNAs has been implicated in cognitive disorders, the task of exploring

the role of lncRNA-mediated epigenetic regulation in normal cognitive function remains incomplete.

Transgenerational impacts of ncRNA-mediated epigenetic regulation

Since the discovery of epigenetics, there has been much curiosity and speculation as to the transgenerational heritability of epigenetic marks. In mammals, much of the epigenome is erased during the processes of fertilization and generation of primary germ cells (reviewed in [170]); nonetheless, evidence of a transgenerationally altered epigenome has steadily accumulated, including heritable cognitive changes and behavioral phenotypes [171–175]. A simple explanation for this phenomenon would be incomplete erasure of DNA and histone modifications. While there is some evidence in support of this hypothesis (reviewed in [176]), other studies have demonstrated the existence of an indirect mechanism of chromatin regulation via generational transfer of ncRNAs.

Recently developed mammalian epimutation models – in which phenotypes are derived from a heritable change in gene expression, as opposed to an altered genome – have demonstrated the sufficiency of parental RNA to alter the epigenome of treated progeny [177]. Additionally, in a rodent stress model, treatment of fertilized mouse oocytes with ncRNAs from the sperm of stressed males is sufficient to recapitulate heritable stress-related behavioral and metabolic phenotypes [173]. These results indicate that alterations in the transcriptome are sufficient for the transfer of epigenetic information across generations, and play a critical role in cognitive function.

The most direct evidence for a neuronal role in transgenerational epigenetic phenomenon comes from *C. elegans*, where neuronally expressed RNA species are transported to the cells of the germline. These RNAs then initiate the transgenerational epigenetic silencing of particular genomic loci, thereby impacting gene expression in the germ line and, potentially, in any progeny [178]. It is tempting to speculate that an analogous mechanism could exist in mammals, by which somatic tissues such as those of the brain may regulate the epigenome of cells distant in both space and time. Clearly, such a finding would have far-reaching consequences for cognitive science.

Conclusion & future perspective

While numerous studies have found associations between ncRNAs, cognition and cognitive disorders, few have fully investigated and characterized the diverse mechanisms that can be attributed to ncRNAs. In this review, we provide insights for future direction in the investigation of different classes of ncRNAs and discuss regulatory RNAs that

have both established roles in cellular and molecular processes and a defined relationship to the epigenome. Thus, we present the provocative research idea that ncRNAs might serve to control epigenetic mechanisms involved in cognition by illustrating the few cases of such phenomena that have been described in the literature.

To date, only a few regulatory RNAs have been discovered to have both epigenetic and cognitive relevance. However, these few examples underscore the extent to which the numerous and heterogeneous classes of regulatory RNAs are still unexplored. Anatomically, these species are expressed primarily within the cognitive centers of the brain, and indeed, their relevance to cognition is well established. However, emerging studies are beginning to explore beyond the canonical pathways of regulatory RNA function established in previous decades. The studies we have reviewed here demonstrate the long-term impact of regulatory RNAs on the epigenome and thereby cognition. Although the canonical functions of ncRNAs involve diverse mechanisms, new insights suggest that several classes of ncRNAs impact the epigenome, a common ground where both protein and RNA species converge to regulate cellular function. Ground-breaking studies are beginning to demonstrate that epigenetic regulation by ncRNAs is – to a yet poorly

explored extent – actively influencing neuronal and cognitive function. Therefore, it is likely that future studies will focus on increasing knowledge of ncRNA-mediated epigenetic regulation on well-characterized cognitive functions, such as memory formation. Moreover, we fully expect that further investigations into the role of regulatory RNAs will reveal novel epigenetic roles for this versatile class of molecules in cognitive disorders.

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Executive summary

- This review discusses mechanisms of multiple classes of noncoding RNAs (ncRNAs) and how they relate to the epigenome.
- Schizophrenia, a cognitive disorder with epigenetic dysfunction, is used to describe a possible role for canonical miRNA species in the regulation of epigenetic mechanisms.
- A description of small interfering RNA mechanism of action is provided, and newly defined mechanisms of epigenetic regulation not yet investigated in cognition or cognitive dysfunction.
- An introduction to PIWI-interacting RNAs is provided along with studies describing the potential role of PIWI-interacting RNAs as regulators of the epigenome in neuroplasticity.
- We present a description of long noncoding RNAs, a newly defined class of ncRNAs, and describe the roles of several long noncoding RNAs in cognition and cognitive disorders. Moreover, we highlight new studies indicating that long ncRNAs impact cognition via their role as epigenetic regulators.
- Importantly, we highlight recent studies on the transgenerational impact of ncRNAs and the epigenome on cognitive function.
- The key findings presented throughout this review warrant future studies of ncRNAs, as related to the epigenome and cognitive function.

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