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Review

Regulation of non-coding RNA networks in the nervous system—What's the REST of the story?

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ABSTRACT

Recent advances are now providing novel insights into the mechanisms that underlie how cellular complexity, diversity, and connectivity are encoded within the genome. The repressor element-1 silencing transcription factor/neuron-restrictive silencing factor (REST/NRSF) and non-coding RNAs (ncRNAs) are emerging as key regulators that seem to orchestrate almost every aspect of nervous system development, homeostasis, and plasticity. REST and its primary cofactor, CoREST, dynamically recruit highly malleable macromolecular complexes to widely distributed genomic regulatory sequences, including the repressor element-1/neuron restrictive silencer element (RE1/NRSE). Through epigenetic mechanisms, such as site-specific targeting and higher-order chromatin remodeling, REST and CoREST can mediate cell type- and developmental stage-specific gene repression, gene activation, and long-term gene silencing for protein-coding genes and for several classes of ncRNAs (e.g. microRNAs [miRNAs] and long ncRNAs). In turn, these ncRNAs have similarly been implicated in the regulation of chromatin architecture and dynamics, transcription, post-transcriptional processing, and RNA editing and trafficking. In addition, REST and CoREST expression and function are tightly regulated by context-specific transcriptional and post-transcriptional mechanisms including bidirectional feedback loops with various ncRNAs. Not surprisingly, deregulation of REST and ncRNAs are both implicated in the molecular pathophysiology underlying diverse disorders that range from brain cancer and stroke to neurodevelopmental and neurodegenerative diseases. This review summarizes emerging aspects of the complex mechanistic relationships between these intricately interlaced control systems for neural gene expression and function.

One of the fundamental questions in neuroscience is how cellular complexity, diversity, and connectivity are encoded within the genome and faithfully elaborated, maintained, and refined during nervous system development, homeostasis, and plasticity. Recent genomic and epigenomic advances are now providing novel insights into the molecular and cellular mechanisms that underlie these processes, including the important and interconnected roles played by the repressor element-1 silencing transcription factor/neuron-restrictive silencing factor (REST/NRSF) and non-coding RNA (ncRNA) networks.

Individual cell types seem to be defined by their expression of a unique repertoire of protein-coding and non-coding transcripts. Studies exploring genomic organization in eukaryotic cells have yielded an increasingly complex view of transcriptional regulation and post-transcriptional processing [9,16,43]. Virtually all of the genome may be transcribed with each nucleotide potentially serving as a multifunctional unit within multiple interleaved and bidirectional genomic elements [9,16,43]. Nonetheless, the transcriptional landscape in each cell and, therefore, cell identity and function are determined with high fidelity throughout development and adult life by a specific series of temporal and spatial extracellular cues, combinatorial transcription factor codes, and fastidious epigenetic regulatory network dynamics. Emerging evidence suggests that REST and its primary cofactor, CoREST, bind to genomic regulatory sequences, including the repressor element-1/neuron restrictive silencer element (RE1/NRSE), where they serve as seminal epigenetic regulators by modulating a large cohort of protein-coding [37,64,72] and non-coding [38,95] genes and pro-

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moting context-dependent gene repression, gene activation, and long term gene silencing [100]. Moreover, REST and CoREST regulatory networks primarily encompass neural genes and are highly integrated with nervous system enriched ncRNA networks that coordinately orchestrate aspects of stem cell maintenance, lineage restriction, neuronal and glial fate specification, terminal differentiation, neural network integration, and activity dependent plasticity [61]. Not surprisingly, perturbations of REST and CoREST activity and related deregulation of ncRNAs have also been implicated in the molecular pathophysiology underlying diverse disorders that range from cancer [10,20,30,34,52,56,65,86,93,94] (i.e., glioblastoma multiforme [GBM], medulloblastoma, and neuroblastoma) and ischemia [14,28] to neurodegenerative (i.e., Huntington's disease [8,40,59,73,101]) and neurodevelopmental (i.e., Down syndrome [15,55], X-linked mental retardation [XLMR] [25,46,47,89], and epilepsy syndromes [7,32]) diseases [70]. This review highlights the increasingly important and context-specific roles that REST and CoREST are thought to play within the nervous system, including the regulation of complex and interrelated ncRNA networks.

REST is a Krüppel type zinc finger transcription factor that binds to genomic sites including but not limited to canonical RE1 sequences, where it acts as a modular scaffold for the assembly of diverse macromolecular complexes. Initially, REST was believed to repress neuronal genes in non-neuronal cells [4,77]. However, a much more complex and nuanced view of REST and its regulatory functions is now emerging because of the increasing number of molecular scaffolds and associated factors that have been shown to either directly or indirectly interact with REST in various cell types and consequently to participate in REST-mediated remodeling of the cellular epigenome. REST recruits two major transcriptional co-regulators, CoREST and mSin3 [2,33]. At its N-terminus, REST recruits mSin3, a scaffold for histone deacetylases (Hdac1, Hdac2, Hdac4 and Hdac5). At its C-terminus, REST partners with CoREST [2], which additionally recruits histone deacetylases (Hdac1 and Hdac2), methyl-CpG binding protein 2 (Mecp2), histone H3K4 lysine demethylase, LSD1, histone H3K9 methyltransferases, G9a and Suv39h1, and a component of the SWI/SNF chromatin remodeling complex, Brg1. In addition, REST also associates with a number of other epigenetic and regulatory cofactors that include other DNA methyltransferases (DNMTs), additional methyl-CpG binding domain proteins (MBDs), chromatin remodeling enzymes, the chromodomain Y chromosome (CDY) family member, CDYL [65], the RNA polymerase II transcriptional Mediator subunits, Med19 and Med26 [24], the NADH-binding factor, CtBP [32], the small C-terminal domain phosphatase, Scp1 [91], and the transcription factor, Sp3 [44]. By acting as an evolving molecular platform to which these diverse factors may all be recruited, REST promotes dynamic modifications of DNA, histones, nucleosomes, and higher-order chromatin codes and helps maintain genomic stability. These gene locus specific and more global epigenetic changes promote context-dependent gene repression, gene activation and long term gene silencing. For example, we recently reported that, in T cells, the association of REST with RE1 sites leads to the removal of several histone modifications that are implicated in dynamic gene activation and to the addition of other modifications associated with heterochromatin associated gene repression [100]. Our study revealed a ubiquitous decline in histone acetylation, while some methylation marks increased (i.e., H3K27me3 and H3K9me2/3) and others decreased (i.e., H3K4me and H3K9me1).

Additional layers of flexibility and specificity are conferred on the activity of the REST complex through several parameters that include its affinity for binding to different RE1 and non-RE1 sites, the deployment of CoREST, the potential for incorporation of alternatively spliced variants of REST [53,54,82,88], the regulation of REST expression and localization [78,80,81], modulation via ncRNAs [50,51,73,91], and emerging post-transcriptional roles for REST [45]. For example, RE1-associated genes may be modulated differentially by the combinatorial actions of distinct REST and CoREST complexes [5]. For a subset of genes, designated as class I genes, only the REST complex binds to their promoter regions. For class II genes, distinct REST complexes and CoREST complexes bind to different sites in their promoter regions. Therefore, class I genes exhibit maximal expression levels when the repressive REST complex is released from their promoters. Conversely, when the REST complex is released from the promoters of class II genes, they exhibit submaximal levels of expression because of the continued presence of a distinct repressive CoREST complex at a different site on their promoters. Moreover, CoREST has been shown to modulate the expression of a subset of RE1 associated genes even in the absence of REST [5]. For class II genes, specific stimuli such as membrane depolarization promote dissociation of MeCP2 and associated cofactors from the CoREST complex, releasing CoREST mediated transcriptional inhibition and permitting maximum class II gene expression [5,6]. The continued presence of CoREST here is interesting because it suggests that CoREST is primed for activity-dependent cofactor recruitment and dynamic transcriptional regulation [5]. Furthermore, CoREST activity is also subject to regulation by post-translational sumoylation, which seems to be necessary for transcriptional repression [66].

Moreover, the REST gene contains three alternative 5′ exons and may also be spliced into four distinct isoforms. Each of these isoforms may be specifically regulated, interact uniquely with RE1s, and have differential effects on nuclear localization, modular function, and gene regulation [53,54,82,88]. For example, REST4 is a truncated isoform of REST that, like REST, binds to the nuclear targeting factor, REST/NRSF-interacting LIM domain protein (RILP) [78], and functions in a dominant-negative manner when coexpressed with REST. It competitively inhibits REST induced gene silencing and promotes gene activation in response to a variety of stimuli [88]. The REST gene locus also contains regulatory elements that may be targeted by several key pathways including Wnt and retinoic acid signaling [69] and Oct4 and Nanog transcriptional networks [39,83]. Further, the REST promoter contains an RE1 sequence suggesting that REST may autoregulate its own expression through this feedback loop. At the protein level, REST is degraded by the E3 ubiquitin ligase, β-TrCP [93]. During the G2 phase of the cell cycle, a β-TrCP-mediated decrease in REST promotes transcriptional derepression of Mad2, which is essential for chromosomal stability and for ensuring the fidelity of mitosis [34]. Moreover, REST nuclear-cytoplasmic trafficking is indirectly controlled by huntingtin (Htt). This trafficking has recently been examined in detail and is carried out by a complex comprised of Htt, which interacts directly with dynactin p150 (Glued) and indirectly with RILP and REST [79]. In addition, small modulatory double-stranded ncRNAs encoding the RE1 sequence (dsNRSEs) have been found in the nucleus where they interact directly with the REST complex to promote transcription of RE1-associated genes [50,51]. This observation highlights the intricate modulatory relationships that link REST function with ncRNA expression and play important roles in the regulation of cell fate in the nervous system (discussed below). Furthermore, a recent study reported a novel role for REST. REST was found to interact with the RE1 sequence of the mu opioid receptor (MOR) gene, to deliver MOR mRNAs to the polyribosome, and to enhance eIF4G phosphorylation promoting translation of MOR protein [45]. This intriguing observation suggests that REST serves not only as a key regulator of transcription but also directly influences post-transcriptional processing of RE1 sequence containing mRNAs.

Because of these myriad layers of embedded regulatory controls, it is attractive to hypothesize that distinct REST and CoREST com-

plexes operate in a coordinated manner to integrate and transduce evolving extracellular and intracellular signals into precise epigenetic changes at genomic sites, thereby establishing, maintaining, and even refining cell- and tissue-specific gene expression profiles.

Genome-wide characterization of promoter regions has revealed that most genes have multiple promoters with a number of possible transcription start sites. In the Encyclopedia of DNA Elements (ENCODE) Project, for example, 81.5% of the genes tested had additional transcription start sites (TSS) that were located either 5′ distal or internal to the annotated gene boundary. Many promoters have also been noted to initiate transcription in both directions with some bidirectional gene pairs exhibiting co-expression while others show more divergent patterns of regulation [9,16,43]. This increasingly complex view of transcription may be particularly relevant for REST-mediated transcriptional regulation in the nervous system, which has high levels of transcriptional activity and ncRNA expression [18,35]. The genome-wide binding profiles for REST have been examined by multiple recent studies. These studies reveal that REST targets the canonical RE1 (cRE1) sequence, which is 21 base pairs, as well as non-canonical RE1 (ncRE1) sequences, which consist of cRE1 sequences that have insertions of variable lengths [72]. These cRE1s and ncRE1s are associated with cell- or tissue-specific hierarchical responses to REST gene regulation [11]. Both cRE1s and ncRE1s are also distributed throughout 5′ and 3′ proximal and distal regulatory sites as well as in intergenic (intronic) regions harboring protein-coding genes and potentially several classes of ncRNAs (e.g., microRNAs [miRNAs] and long ncRNAs).

REST was initially found to modulate a subset of genes that are essential for neuronal differentiation, homeostasis and plasticity including growth factors, cytokines, ion channels, neurotransmitter receptors, cell adhesion molecules, axonal guidance cues, and synaptic vesicle proteins [17]. Indeed, the expression of neuronal genes and, in turn, neuronal identity is partially controlled by REST, which acts in concert with other control systems such as miRNA networks. Like REST, miRNAs are regulatory molecules implicated in neuronal differentiation, maintenance, and plasticity [71]. miRNA expression profiles are highly developmentally regulated and cell type-specific, with certain miRNAs only expressed in the brain (i.e., *miR-124*, *miR-128* and *miR-9*) [71]. miRNAs suppress expression of their target genes through post-transcriptional mechanisms. They directly interact with the 3′ untranslated region (UTR) of target mRNAs leading to translational repression and sequestration in P-bodies for storage or degradation. P-bodies are cytoplasmic RNA containing structures that control mRNA turnover and translational repression and also participate in trafficking of RNAs to dendrites regulating translation as well as synaptic plasticity [96,97].

Although the regulatory networks that influence miRNA expression and function are largely unknown, a significant subset of RE1 sites are within the vicinity of nervous system enriched miRNA genes, and REST regulates the expression of these miRNAs [95]. Also, REST potentially modulates genes critical for miRNA biogenesis and function such as *Dicer1*, *Ago1*, *Ago3*, *Ago4* and *Xpo5*, which are all RE1 associated [69]. Further, REST and potentially members of the REST complex are also targets of multiple miRNAs, including *miR-124*, *miR-9*, and *miR-132* [73,95], implying that these intricate transcriptional and post-transcriptional regulatory controls for neuronal gene expression are highly integrated and mediated, in part, by double-negative feedback loops between REST and the miRNAs. In addition, many of these miRNA genes also contain cAMP response elements (CREs) in their regulatory regions, suggesting that the transcriptional regulator cAMP response element-binding protein (CREB) is also integrated into REST-miRNA regulatory networks that mediate neural gene expression programs [95].

miRNAs are not the only class of ncRNAs that are REST targets. By applying an unbiased algorithm to scrutinize the genomic distribution of RE1 sites and ncRNA genes, a recent study found that 23% of REST binding sites are within 10 kb of long ncRNA genes [38]. *In vitro* studies confirmed that REST modulates the expression of some of these ncRNAs. In the human genome, REST binds to a proximal upstream binding site of the DiGeorge syndrome-associated ncRNA (*DGCR5*) resulting in transcriptional repression. Of note, the *DGCR5* locus is a breakpoint region in DiGeorge syndrome, which is characterized by developmental malformations and neuropsychiatric disorders. Similarly, in the mouse genome, two candidate long ncRNAs, *AK046052* and *AK090153*, are clearly regulated by REST, while flanking protein-coding genes are only weakly influenced by REST, suggesting that REST specifically targets these long ncRNAs. Both of these long ncRNAs are developmentally expressed and restricted to the nervous system similar to other REST targets that represent protein-coding and miRNA genes [38]. Recent studies have suggested that mammalian genomes encode thousands of these long ncRNAs, of which many happen to be polyadenylated, developmentally regulated, environmentally responsive, alternately spliced, nervous system enriched, and rapidly evolving. Long ncRNAs exhibit developmentally regulated temporal, spatial, and cell type specific expression profiles in the mouse brain [63] and embryonic stem cells (ESCs) [26]. These ncRNAs have been implicated generally in the regulation of chromosomal architecture and dynamics, transcription, post-transcriptional processing, and RNA editing and trafficking [61] and specifically in modulation of the epigenetic status of nearby protein-coding genes, by recruiting chromatin activator or repressor complexes to their target loci [60]. For example, the imprinted ncRNA, *Air*, accumulates at promoter regions where it silences gene expression by recruiting the H3K9 methyltransferase, G9a [67].

As the complexity of genomic organization and the intricate layers of functional transcripts that are embedded within the genome become increasingly apparent, a deeper understanding of both local and global epigenomic regulation is necessary to account for the distinct temporal, spatial, and tissue-specific expression patterns of these mRNAs and heterogeneous classes of ncRNAs. These include but are not limited to miRNAs, small nuclear RNAs (snRNAs), small nucleolar RNAs (snoRNAs), antisense RNAs, (asRNAs), long ncRNAs, as well as other emerging ncRNA subclasses. We suggest that, because of their cell type specificity, functional plasticity, and capacity for site-specific and genome-wide epigenetic regulation of protein-coding and non-coding genes, REST and CoREST may be important for mediating dynamic interactions between genomic organization, nuclear architecture, and transcription in a developmentally regulated and environmentally responsive manner. Indeed, REST and CoREST may encode and transduce epigenetic signals by modulating chromatin structure and local and long-range biophysical dynamics. These factors may play a vital role in executing varied genomic programs such as local and long-range interconnected transcriptional regulation, interallelic communications, spatial arrangement of genomic sequences, and higher-order regulatory DNA conformations within different nuclear microdomains. Therefore, the dynamics of REST and CoREST may also have important implications for understanding how nuclear, cytoplasmic and synaptic events participate in the coordination of neural development, homeostasis, and plasticity.

REST has been implicated in cell- and tissue-specific epigenetic modulation in a developmental stage-specific manner. It is also increasingly clear that REST and CoREST are both crucial not only in neural stem cells (NSCs) and non-neuronal cells, as was initially characterized, but specifically in embryonic stem cells (ESCs), lineage restricted neuronal and glial progenitors, and in terminally differentiated neurons and glia.

ESC chromatin is poised for transcription, and genes encoding factors important for germ layer specification are functionally primed through bivalent chromatin domains (i.e., H3K4me3 and H3K27me3) [31]. Differentiation into a specific lineage leads to silencing of genes that are involved in pluripotency and in specification of alternate lineages. Intriguingly, one key feature of REST transcriptional networks is that they are highly integrated with the transcriptional networks of the core pluripotency factors—Oct4, Sox2, and Nanog [12,41,83]. In fact, a controversy has erupted over the potential role of REST in maintaining self-renewal and pluripotency in ESCs. In one study, REST was found to regulate miRNAs that potentially target self-renewal genes (i.e., *miR-21*), and heterozygous deletion of REST in mouse ESCs led to reduced expression of pluripotency markers including Oct4, Nanog, Sox2, and c-Myc [83], suggesting that REST mediates ESC pluripotency. In contrast, other studies showed that haplodeficient REST ESCs exhibited no significant change in pluripotency markers [12] and that loss of functional REST protein did not restrict ESC lineage potential and self-renewal capacity [41], demonstrating that REST is not required for ESC pluripotency. Despite the potential role that REST may play in the regulation of pluripotency networks, it does appear to silence a subset of RE1 associated genes in ESCs, including those that are important for neuronal terminal differentiation and function (i.e., *Scg3*, *Stmn3*, *Celsr3*, *Syp*, *Cplx1*, and *Syt4*) but not those that are crucial for promoting neural commitment of ESCs (i.e., *Mash1* and *Math1*) [42]. This observation suggests that, in ESCs, REST does not repress the potential for neural lineage commitment but suppresses gene expression programs responsible for neuronal subtype specification.

These gene expression programs are subsequently activated during neurogenesis, and REST may dynamically regulate these gene expression programs as well. In fact, in rat adult hippocampal NSCs, REST interacts with small modulatory ncRNAs encoding the RE1 sequence (dsNRSEs), which transform the REST complex into a transcriptional activator and induce neuronal differentiation [50,51]. Moreover, REST-deficient NSCs exhibit defective adherence, migration and survival, which may be rescued by exogenous laminin, highlighting the role of REST in extracellular matrix regulation during neural differentiation [87]. Despite these key functions, levels of REST protein have been noted to decrease during NSC differentiation, partly through proteasomal degradation [93]. This downregulation of REST expression may be important because REST also regulates the expression of certain miRNAs, including the nervous system specific *miR-124*, which suppresses hundreds of non-neuronal genes. In non-neuronal cells and in neural progenitors, REST represses *miR-124* [95]. However, when progenitors differentiate into mature neurons, REST is down regulated and consequently *miR-124* is de-repressed leading to the degradation of non-neuronal transcripts.

While these examples support the conclusion that the REST regulon operates in a developmental stage-, cell-, and tissue-specific manner, recent studies have started to identify the specific components of REST and CoREST regulatory networks in developmental cell types. Comparing profiles of REST target genes in ESCs and in NSCs reveals that these profiles are distinct but overlapping, with specific sets of genes subject to REST-mediated transcriptional regulation in each cell type [39]. Furthermore, our recent studies of forebrain derived NSC-mediated lineage elaboration have uncovered cell type specific profiles for REST and CoREST target genes in an integrative neural developmental paradigm. Our observations suggest for the first time that REST and CoREST play instrumental roles in regional neuronal subtype specification as well as in glial lineage specification including promoting progressive stages of oligodendrocyte (OL) lineage maturation including myelination. Moreover, our findings also indicate that CoREST may preferentially mediate NSC maintenance and maturational functions. These studies have identified thousands of new developmental stage- and lineage-specific REST and CoREST target genes that mediate a spectrum of critical and complementary biological functions.

Emerging evidence suggests that REST plays a role in the molecular pathophysiology underlying diverse disorders [70], though many questions remain regarding the implications of altered REST levels and functions for deregulation of ncRNAs and modulation of other epigenomic mechanisms. For example, REST inactivation (i.e., dominant-negative isoforms and frame-shift mutations of REST), overexpression, and copy number variation are all observed in various cancer phenotypes, implying that REST has paradoxical functions as both a tumor suppressor gene and an oncogene depending on the cellular environment [56,92,94]. The mechanisms through which REST promotes cellular transformation are now beginning to be characterized and are consistent with its multifaceted cellular roles. They include β-TrCP-mediated deregulation of REST, which causes global genomic instability and promotes proliferation of developmentally immature tumor cells [34,93]. In addition, recent studies show that an increasing number of REST regulated miRNAs are deregulated in different cancers, especially those within the nervous system (i.e., neuroblastoma, medulloblastoma, and GBM) [13,68,84,98], leading to silencing of tumor suppressor genes, activation of oncogenes, and deregulation of stem cell self-renewal and specification genes. REST is similarly implicated in the pathogenesis of Huntington's disease (HD) [8,40,59,73,101], which is caused by an abnormal expansion of trinucleotide repeats in the Htt gene and is characterized by extensive transcriptional dysregulation. Mutant Htt allows REST to be inappropriately transported into the nucleus resulting in aberrant nuclear accumulation of REST and deregulation of REST target gene expression. In fact, a recent study showed that REST promoter occupancy is increased even in peripheral lymphocytes from HD subjects [59]. Moreover, a number of REST regulated miRNAs are also deregulated in both animal models of HD and human HD [40,73]. Among these is the brain enriched *miR-9*/*miR-9**, which targets both REST (*miR-9*) and CoREST (*miR-9**), providing an example of a double negative feedback loop between REST (and CoREST) and a bifunctional miRNA that is perturbed in HD [73]. The complex crosstalk between the REST-, Htt-, and ncRNA-mediated mechanisms that underlie transcriptional and post-transcriptional deregulation in HD is further highlighted by the observation that Htt, itself, binds to Ago2 and localizes to P-bodies where it contributes to RNA-mediated gene silencing [76]. The expression and function of REST are also disturbed in Trisomy 21/Down syndrome (DS), the most frequent cause of mental retardation [15,55]. The RE1 associated DYRK1A gene, which is located in the Down syndrome critical region, is strongly implicated in the pathogenesis of neural defects, in part, because it perturbs REST levels [15] and REST-SWI/SNF chromatin remodeling complex interactions [55]. In addition, increased dosage of DYRK1A disrupts CREB and NFATc-calcineurin regulatory circuits, which include many members (i.e., *Nfatc1*, *Nfatc2*, and *Nfatc4*) that are also RE1 associated [75]. Furthermore, DS is associated with overexpression of various miRNAs located on chromosome 21, including *miR-99a*, *let-7c*, *miR-125b-2*, *miR-155*, and *miR-802* [49].

These observations highlight how aberrant REST (and possibly CoREST) activity may be involved in the molecular pathogenesis of various classes of neurological disease including cancer and neurodegenerative and neurodevelopmental disorders, which exhibit diverse profiles of alterations in the proper establishment and maintenance of cell identity and connectivity; regulation of cell cycle progression, arrest, and exit; modulation of apoptosis; and promotion of homeostasis and plasticity that are intimately linked to changes in ncRNA expression and function.

We are just now beginning to recognize the wide range of context-specific roles played by REST and CoREST in regulation of

the neural epigenome. Indeed, it is becoming increasingly clear that REST and CoREST are critical for modulating the dynamic expression and function of a broad array of protein-coding and non-coding transcripts through cell- and tissue-specific regulation of diverse processes, including transcription and post-transcriptional processing. In addition, it seems possible and even likely that REST and CoREST mediate additional epigenomic programs, which may similarly promote the elaboration, maintenance, and refinement of cellular complexity, diversity, and connectivity in the nervous system. These may include cell- and tissue-specific regulation of alternative splicing; temporal, spatial, and activity-dependent localization of RNA species; RNA editing; and intercellullar trafficking of mRNAs and ncRNAs. While the roles played by REST and CoREST in the orchestration of these diverse and essential biological processes have not been studied in detail, recent advances raise the possibility that REST and CoREST and their dynamic interplay with ncRNAs are important for the execution of these processes.

For example, proper alternative RNA splicing is crucial for the development of the nervous system and may be governed both by REST and by ncRNAs. The neuronal *miR-124* directly targets *Ptbp1*, which is a repressor of alternative pre-mRNA splicing in non-neuronal cells [57]. During neuronal differentiation, *miR-124* down regulates *Ptbp1* leading to an increase in *Ptbp2*, its nervous system enriched homolog, which promotes neuron specific alternative splicing patterns [57]. Intriguingly, *miR-124* is REST-regulated [95], *Ptbp1* is RE1 associated, and *Ptbp2* is targeted by REST and CoREST during neural lineage elaboration. REST and/or CoREST also bind to a variety of other factors with roles in neuronal splicing (i.e., *Nova2*) [64]. Moreover, REST, itself, has multiple isoforms that may have synergistic and/or antagonistic effects within the regulatory mechanisms for alternative splicing [21,48,53,54,74,82]. These observations strongly suggest that alternative splicing is governed by a complex network of regulatory mechanisms, which include a series of highly integrated feedback relationships between REST, CoREST, and ncRNAs.

Furthermore, additional post-transcriptional processing and transport are extremely important for the appropriate temporal, spatial, and activity-dependent localization and function of RNAs within neural cells; and, these processes are mediated by specialized RNA operons and RNA regulons whose composition and function may be influenced, in part, by REST, CoREST, and related ncRNAs [1,27,58,60,62]. RNA operons refer to complexes consisting of functionally related protein-coding RNAs and ncRNAs along with trans-acting factors that include RNA binding proteins (RBPs) and other RNA interactors such as argonaute proteins, which act as hubs for co-regulation of RNAs within neuronal granules that subserve RNA splicing, editing, nuclear export, stabilization, localization and translation. RNA regulons represent additional regulatory mechanisms that coordinate higher-order dynamics of groups of RNAs and RNA operons in a combinatorial fashion by modulating their contents, anterograde and retrograde axodendritic transport, and additional functional features. Studies suggest that REST and CoREST regulate genes implicated in many aspects of the formation and functioning of these RNA operons and RNA regulons. For example, we found that, during neural lineage elaboration, REST and/or CoREST differentially targeted genes associated with nuclear microdomains called paraspeckles (i.e., *Pspc1*, *Sfpq* and *Sfrs11* [*p54*]) whose protein products bind both DNA and RNA and are implicated in alternative splicing, transcriptional regulation, and nuclear retention of edited transcripts [19]. Specifically, Sfrs11 directly binds adenosine-to-inosine hyperedited RNAs and retains them in the nucleus [99]. Rbm14 is another paraspeckle protein that couples alternative splicing with transcription [3,29]. Although Rbm14 is associated with an RE1 sequence, neither REST nor CoREST bound to it in our studies further implying a high degree of context-specific epigenomic regulation of paraspeckle genes. Intriguingly, the Pspc1 and Sfrs11 proteins directly associate with *NEAT1*, which is a long polyadenylated ncRNA that serves as the primary architectural component defining paraspeckle structures [19]. Further, we also found that REST and/or CoREST targeted a multitude of other factors including but not limited to RBPs involved in RNA processing, transport, and metabolism (i.e., *Stau2* and *Cugbp1*), RNA editing enzymes (i.e., *Adar2*, *Adar3*, *Apobec1*, *Apobec2*, and *Aicda*), nuclear export factors (i.e., *Nxf1* and *Nxf2*), and members of the kinesin and dynein families of molecular transport motor proteins. Together, these findings strongly suggest that post-transcriptional processing and transport of RNAs are mediated by a diverse group of factors, which are subject to epigenomic modulation by REST and CoREST.

Myriad aspects of protein-coding RNA and ncRNA post-transcriptional processing, trafficking, and functional regulation seem to be modulated by REST and/or CoREST within neural cells, and emerging evidence suggests that REST and CoREST also regulate local and more distant intercellular communication, including that which is mediated by ncRNAs [27]. In fact, REST governs the expression of ion channels, neurotransmitter receptors, gap junctions, and neurosecretory vesicles [22,23]. These mechanisms for cell–cell communication may also act as dynamic intercellular functional, regulatory and signaling mechanisms for RNA species. For example, microvesicles (i.e., exosomes) are secreted by many cell types, including those in the nervous system, and circulate in the peripheral blood. These secretory exosomes may contain both mRNAs and ncRNAs and may express cell recognition molecules on their surface for selective targeting and uptake into recipient cells [36,84,85,90]. Activity-dependent epigenetic modulation of cell–cell communication through local and more long-distance trans-neuronal RNA transfer and recipient cell processing may be particularly important for regulating anterograde and retrograde signaling across synapses, reinforcing local and long-range neural network connectivity, and promoting oscillatory synchrony, the substrate for orchestrating higher-order cognitive and behavioral repertoires [27,62].

Future studies are necessary to characterize exactly how REST and CoREST modulate the neural epigenome to orchestrate cell- and tissue-specific transcription; post-transcriptional RNA processing; temporal, spatial, and activity-dependent localization of RNA species; RNA editing; and intercellular trafficking of gene products. These studies will be important not only for understanding the production and cultivation of cellular diversity and connectivity in the nervous system but also for understanding disease pathogenesis, discovering more sensitive and specific biomarkers for disease onset and progression, and developing novel epigenomic reprogramming strategies that focus on preventing disease and restoring neurological function.

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