Published in final edited form as:

Neuroscience. 2014 April 4; 0: 131–141. doi:10.1016/j.neuroscience.2013.06.051.

Chromatin-bound RNA and the Neurobiology of Psychiatric Disease

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Abstract

A large, and still rapidly expanding literature on epigenetic regulation in the nervous system has provided fundamental insights into the dynamic regulation of DNA methylation and post-translational histone modifications in the context of neuronal plasticity in health and disease. Remarkably, however, very little is known about the potential role of chromatin-bound RNAs, including many long non-coding transcripts and various types of small RNAs. Here, we provide an overview on RNA-mediated regulation of chromatin structure and function, with focus on histone lysine methylation and psychiatric disease. Examples of recently discovered chromatin-bound long non-coding RNAs important for neuronal health and function include the Brain-derived Neurotrophic Factor antisense transcript (*Bdnf-AS*) which regulates expression of the corresponding sense transcript, and *LOC389023* which is associated with human-specific histone methylation signatures at the chromosome 2q14.1 neurodevelopmental risk locus by regulating expression of *DPP10*, an auxiliary subunit for voltage-gated K(+) channels. We predict that the exploration of chromatin-bound RNA will significantly advance our current knowledge base in neuroepigenetics and biological psychiatry.

Introduction

Epi-(greek for ‘over’, ‘above’) *genetics*, with the more traditional definition equated with heritable changes in gene expression and function in the absence of DNA sequence alterations, is nowadays a much more broadly applied concept describing the regulation and organization of chromatin structures in dividing and postmitotic cells. Consequently, epigenetics is presently reshaping our thinking of normal brain development and function, and the neurobiology of psychiatric disease. It is now generally accepted that the epigenetic landscape remains ‘plastic’ throughout all periods of the developing and aging human brain, with ongoing dynamic regulation even in neurons and other postmitotic constituents (Siegmund et al., 2007, Cheung et al., 2010, Hernandez et al., 2011, Numata et al., 2012, Shulha et al., 2013). Furthermore, disordered chromatin organization and function could be a key pathology not only in several neurodevelopmental syndromes of early childhood, but also in a subset of adult onset hereditary neurodegenerative disorders (Jakovcevski and

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The authors report no conflict.

Akbarian, 2012). The enormous interest in chromatin-associated mechanisms in the context of normal and abnormal plasticity in the developing and mature brain has given rise to a new discipline, 'neuroepigenetics' (Day and Sweatt, 2010). Curiously, however, while there is a large, and still rapidly expanding literature on dynamic changes in DNA methylation, post-translational histone modifications and variants in preclinical model systems of cognitive or psychiatric disease, very little is known about the role of chromatin-bound RNAs (CBRs). While the process of gene expression is obviously defined by nascent RNA emerging from genomic DNA packaged into chromatin, the term CBR should only apply to RNA species as part of a chromatin structure, thereby regulating its functions. According to some estimates, up to 2–3% of the nucleic acid content in chromatin is contributed by polyadenylated RNAs (Rodriguez-Campos and Azorin, 2007), including many long non-coding (nc)RNAs, commonly defined by a minimum length of 200bp and the absence of an open reading frame for protein translation, and additional smaller RNA species. Because many of the recently functionally characterized CBRs are associated with the regulation of histone methylation, we will begin this review with an introduction on the role of histone methylation in normal brain development and in the context of cognitive and psychiatric disease, followed by a discussion on the various types of non-coding RNA that are involved in the regulation of chromatin structure and function. We then will discuss three examples of specific long ncRNAs with pivotal importance for the neurobiology of cognition and disease, including the (1) brain-derived neurotrophic factor (*Bdnf*) antisense transcript, *Bdnf-AS* (Modarresi et al., 2012), (2) a human-specific non-coding RNA, *LOC389023*, which recently was linked to the emergence of human-specific histone methylation signatures in prefrontal cortex neurons (Shulha et al., 2012b), and (3) a very large ncRNA (*SNRPN-UBE3A*) at the *chromosome 15q11-13* Prader Willi and Angelman Syndrome imprinting locus which contributes to an extremely complex and multilayered process of epigenetic regulation (Leung et al., 2011). We predict that in the nearby future, the study of CBRs will further fuel the current interest in neuroepigenetics and fertilize current concepts on the neurobiology of neurological and psychiatric disease.

Histone methylation and epigenetic regulation in the nervous system

Chromatin is defined by arrays of nucleosomes, or 146 bp of genomic DNA wrapped around an octamer of core histones H2A, H2B, H3 and H4, connected by linker DNA and linker histones. The combined set of covalent DNA & histone modifications and variant histones provide the major building blocks for the 'epigenome', or the epigenetic landscapes that mold and organize DNA into distinct transcriptional units, condensed chromatin (often equated with the term 'heterochromatin') and many other features that distinguish between various cell types and developmental stages sharing the same genome (Li and Reinberg, 2011, Rodriguez-Paredes and Esteller, 2011). From a broad perspective, chromatin is ultimately the critical substrate through which genetic information intersects with cell physiology and the environment.

There are more than 100 amino acid residue-specific post-translational modifications (PTMs) of the core histones in a typical vertebrate cell (Tan et al., 2011), including mono (me1), di (me2)- and tri (me3) methylation, acetylation and crotonylation, polyADP-ribosylation and small protein (ubiquitin, SUMO) modification of specific lysine residues, as well as arginine (R) methylation and 'citrullination', serine (S) phosphorylation, tyrosine (T) hydroxylation, among others (Kouzarides, 2007, Taverna et al., 2007, Tan et al., 2011). These site- and residue-specific PTMs show close association with the functional architecture of chromatin, differentiating between promoters and gene bodies, enhancer and other regulatory sequences and heterochromatin (Zhou et al., 2011). The modifications do not occur in isolation, and instead multiple histone PTMs appear to be co-regulated and, as a group define the aforementioned chromatin states. For example, both histone H3 lysine 4

methylation and various histone acetylation markings are up-regulated at many transcription start sites of actively expressed genes (Zhou et al., 2011). Furthermore, there is also evidence for a coordinated and sequential regulation; for example, phosphorylation of histone H3 at the serine (S)10 position often serves as a prelude for subsequent acetylation of neighboring lysine residues K9 and K14 in the context of transcriptional activation, while at the same time blocking repression-associated methylation of H3 K9 (Nowak and Corces, 2004).

There are an estimated 100 lysine and arginine residue-specific histone methyltransferases and demethylases encoded in the genome, which would suggest that these types of modifications are among the most highly regulated epigenetic markings. (Copeland et al., 2009). To date, at least 20 methyl-marks on K and R residues have been described (Kouzarides, 2002, Mosammaparast and Shi, 2010, Tan et al., 2011). As it pertains to the lysines, the majority of studies focused on six specific sites: H3K4, H3K9, H3K27, H3K36, H3K79 and H4K20 (Mosammaparast and Shi, 2010).

Regulation of histone methylation in the context of cognition and neuropsychiatric disease

Histone H3 at lysine 4

Monomethylation of histone H3-lysine 4 (H3K4me1) plays an important role for neuronal activity-induced transcription at enhancer sequences (Kim et al., 2010). The higher methylation forms of H3K4, H3K4me3 and H3K4me2 are primarily found at the 5' end of genes, with H3K4me3 mostly arranged as distinct and sharp peaks within 1–2Kb of transcription start sites. The H3K4me3 mark provides a docking site at the 5' end of genes for chromatin remodeling complexes that facilitate, and at some sites, repress transcription (Shilatifard, 2008).

The first H3K4-specific histone lysine (K) Methyl-Transferase (KMT) explored in the nervous system was KMT2A/MLL1, a member of the mixed-lineage leukemia (MLL) family of molecules. Mice heterozygous for an insertional (lacZ) loss-of-function *Mll1* mutation show distinct abnormalities in hippocampal plasticity and signaling (Kim et al., 2007), in conjunction with defects of learning and memory (Gupta et al., 2010). Furthermore, conditional deletion of *Mll1* resulted in defective neurogenesis during the early postnatal period (Lim et al., 2009). While the full spectrum of MLL1 target genes in neurons and glia awaits further investigation, dysregulated expression of certain transcription factors such as DLX2, a key regulator for the differentiation of forebrain GABAergic neurons (which are essential for inhibitory neurotransmission and orderly synchronization of neural networks) (Anderson et al., 1999), could contribute to the cognitive phenotype of the *Mll1* mutant mice. These observations may be relevant for the pathophysiology of schizophrenia, because some patients show in the prefrontal cortex a deficit in H3K4-trimethylation and gene expression at a subset of GABAergic promoters, including *GAD1* encoding a GABA synthesis enzyme (Huang et al., 2007). *Mll1* is not the only H3K4-specific KMT important for higher brain function, and hippocampal ablation of a related gene, *Mll2*, also causes learning and memory defects (Kerimoglu et al., 2013). Furthermore, loss-of-function mutations in *KDM5C/JARID1C/SMCX*, encoding an X-linked lysine (K) De-Methylase (KDM) specific for H3K4, are a cause of intellectual disability (Jensen et al., 2005, Santos et al., 2006, Tzschach et al., 2006, Tahiliani et al., 2007, Abidi et al., 2008) and autism (Adegbola et al., 2008). The *KDM5C* gene product operates in a chromatin remodeling complex together with HDAC1/2 histone deacetylases and the transcriptional repressor REST, thereby poisoning neuron-restrictive silencer elements for H3K4 demethylation and decreased expression of target genes including synaptic proteins and sodium channels

(Tahiliani et al., 2007). Given this context a recent postmortem brain study explored H3K4me3 landscapes separately in neuronal and non-neuronal nuclei collected from 31 subjects from the late gestational period to 80 years of age (Shulha et al., 2013). In neuronal chromatin, the H3K4me3 mark was developmentally regulated at > 1,000 loci, including 800 that were within a few kilobases from annotated transcription start sites. Interestingly, the overwhelming majority and perhaps all of developmentally regulated H3K4me3 peaks in neurons were on a unidirectional trajectory defined by either rapid gain or loss of histone methylation during the late prenatal period and the first year after birth, followed by similar changes but with progressively slower kinetics during early and later childhood and only minimal changes later in life (Shulha et al., 2013). Developmentally downregulated H3K4me3 peaks in prefrontal neurons were enriched for Paired box (Pax) and multiple Signal Transducer and Activator of Transcription (STAT) motifs, which are known to promote glial differentiation. In contrast, H3K4me3 peaks subject to a progressive increase in maturing prefrontal neurons were enriched for activating protein-1 (AP-1) recognition elements that are commonly associated with activity-dependent regulation of neuronal gene expression (Shulha et al., 2013). These findings would suggest that maturation of the prefrontal cortex is associated with a pre-programmed, genome-wide remodeling neuronal H3K4 methylation, with the dramatic changes during perinatal period and early childhood development followed by a much slower pace during subsequent years. This finding resonates with the aforementioned genetics literature linking mutations in H3K4-specific demethylase *KDM5C* to neurodevelopmental disease and further underscores that the neurons of the immature brain are particularly vulnerable to defects in the regulation of H3K4 methylation. Of note, prefrontal neurons of a subset of cases on the autism spectrum (autism is considered a highly heterogeneous neurodevelopmental syndrome that shares core deficits in social cognition and communication, and typically diagnosed in early childhood) showed excess, or loss, of H3K4 trimethylation at numerous genomic risk loci linked to the disease, suggesting that epigenetic and genetic risk architectures of autism show significant overlap (Shulha et al., 2012a). Taken together, these clinical studies resonate nicely with the preclinical work in mice and further strengthen the notion that proper regulation of H3K4 methylation in immature cortical neurons is pivotal importance for neuronal health and function later in life.

H3K27

While the mono-methylated form of H3-lysine 27 is enriched in gene bodies of highly expressed genes in some tissues and cell types, including the erythroid system (Steiner et al., 2011), the di- and trimethylated forms are some of the best studied histone marks associated with gene silencing, repression and heterochromatinization (Beck et al., 2010, Justin et al., 2010, Zhou et al., 2011). The H3K27 - specific histone methyltransferase KMT6A, also known as Enhancer of zeste homolog2 (EZH2), is associated with the polycomb repressive chromatin remodeling complex 2 (PRC2) (Herz and Shilatifard, 2010). The PRC2 complex is essential for cortical progenitor cell and neuron production and loss of EZH2 function is associated with severe thinning of the cerebral cortex and a disproportionate loss of neurons residing in upper cortical layers I–IV (Pereira et al., 2010). Likewise, the H3K27-specific demethylase, JMJD3, is important for neurogenesis and neuronal lineage commitment (Burgold et al., 2008). Furthermore, H3K27 methylation is dynamically regulated in mature brain and involved in the neurobiology of major psychiatric disease. For example, changes in expression of brain-derived neurotrophic factor (*Bdnf*) in hippocampus of mice exposed to environmental enrichment or chronic stress are associated with opposite changes in the H3K27me3 mark at a subset of *Bdnf* gene promoters (Tsankova et al., 2006, Kuzumaki et al., 2010). In addition, acute stress leads to an overall decrease in hippocampal H3K27me3 and H3K9me3 (Hunter et al., 2009). Furthermore, in the orbitofrontal cortex of suicide completers, alterations in H3K27 methylation were described at the *TRKB* gene, encoding

the high affinity receptor for the nerve growth factor molecule, BDNF (Ernst et al., 2009). Changes in the balance between histone H3K4 and H3K27 methylation, or DNA cytosine and H3K27 methylation may also contribute to GABAergic gene expression deficits in schizophrenia (Huang and Akbarian, 2007, Huang et al., 2007). To date it remains unclear which of the various H3K27-specific KMTs and KDMs (Fig. 1) are involved in these disease-related alterations in postmortem brain tissue. Of note, the *Jumonji and Arid containing protein 2* (JARID2), which by itself lacks catalytic activity but facilitates methylation by recruiting the polycomb PRC2 complex to its target genes (Li et al., 2010, Pasini et al., 2010), is located within the schizophrenia susceptibility locus on chromosome 6p22 and confers genetic risk in multiple populations of different ethnic origin (Pedrosa et al., 2007, Liu et al., 2009). In addition, *JARID2* mutations and structural variants were recently linked to neurodevelopmental disease including autism and intellectual disability (Bureau et al., 2011, Celestino-Soper et al., 2012, Ramos et al., 2012, Di Benedetto et al., 2013). While the biological functions of JARID2 have been studied primarily in the context of transcriptional regulation in stem cells (Peng et al., 2009, Shen et al., 2009), *JARID2* shows widespread expression in the mature nervous system (Lein et al., 2007), implying JARID2-mediated control over polycomb repressive chromatin remodeling in the adult brain.

Epigenetic and transcriptional regulation by non-coding RNAs (ncRNA) – An Overview

Two independent lines of discovery have permanently changed the until recently widely held view which implicated RNA as mere intermediate in the flow of genetic information from gene to protein. One line of research emerged from the discovery that double-stranded RNAs (dsRNAs) can efficiently silence gene expression in *Caenorhabditis elegans*, a phenomenon now commonly referred to as RNA interference (RNAi) (Fire et al., 1998). A second line of research unfolded when the archetype of long ncRNA, the *X-chromosome Inactive Transcript* (*XIST*), was linked to repressive, PRC2-mediated chromatin remodeling (Zhao et al., 2008, Brockdorff, 2013). Thus, it is now well accepted that RNA is not merely a structural and intermediate component of that central ‘gene to protein’ dogma, and instead RNA emerged as a new frontier for understanding epigenetic and transcriptional regulation (Lozada-Chavez et al., 2011, Altman, 2013). Such regulatory and epigenetic role of RNA intermediates has been further strengthened and revisited by recent findings that almost in each cell type, the vast majority, or up to 80 % of the genome are transcribed and associated with regulatory chromatin associated with gene expression or silencing across model organisms and at various development and disease states (Birney, 2012, Pennisi, 2012). Of note, the majority of these newly discovered RNA species do not encode protein (Luco and Misteli, 2011, Mattick, 2011). Importantly, despite of a large number of studies on epigenetic regulation in the nervous system, the role of non-coding RNAs (ncRNAs) and their direct or indirect role in regulating gene expression and chromatin structures in the brain has barely been explored. Here, we provide a general overview on ncRNAs and then discuss specific examples of ncRNAs in the brain associated with the regulation of chromatin structure and function in the brain.

There are two major classes of ncRNAs: small RNAs that typically range from ~20 – 30 nucleotide long and longer ncRNAs that range from 100nt – >100kb long (Ghildiyal and Zamore, 2009, Malone and Hannon, 2009). The most commonly applied arbitrary definition for long ncRNAs applies a cut-off of 200 nucleotide as minimum length (Hung and Chang, 2010). Small RNAs are further divided into 3 different classes based on their mechanism of biosynthesis, target complementarity and source of precursor. 1. microRNAs (miRNAs) are hairpin derived RNAs and are not perfectly complementary to target sequence, and mediate

translational repression and non-specific RNA sequestration (Bartel, 2004). 2. Small interfering RNAs (siRNAs) have perfect complementarity to target sequence and mediate transcript cleavage and degradation (Karagiannis and El-Osta, 2004). 3. Piwi interacting RNAs (piRNAs) are longer among these three classes (~24–30nt long vs ~20–22nt long), and typically target transposons and repetitive sequences in the germ line (Ishizu et al., 2012). All three types of small RNAs direct Argonaute proteins, the catalytic component of RNA induced silencing complex (RISC) to cleave complementary target RNAs at the phosphodiester bond present between target nucleotide sequences (Filipowicz, 2005). Apart from their endonucleotic function, many small as well as some longer ncRNAs play a potential role for the RNA-induced transcriptional silencing complex (RITS) associated with the regulation of chromatin in yeast (*S. Pombe*) pericentromeric regions, flies, plants as well as animals models (Grewal and Jia, 2007, Grewal, 2010). In yeast, the RITS interacts with methylation of histone H3 at lysine 9 (an epigenetic mark commonly associated with repressive chromatin) and contributes to heterochromatin formation (Verdel et al., 2004). Similarly siRNA directed DNA methylation is well established in *A. Thaliana* (Zhang et al., 2006). In drosophila ovaries, piRNAs defend against wide variety of transposable elements using primary piRNA input sequences from piRNA clusters as well as PIWI (piRNA argonaute) proteins directed against H3K9 methylation to repress transcription start sites of various transposons and other jumping genes to prevent their mobilization (Guzzardo et al., 2013) (Aravin et al., 2007a). PIWIs also interact with heterochromatin-associate protein 1 (HP1) as well as other epigenetic regulators important for maintaining silenced chromatin state (Brower-Toland et al., 2007). MIWI2, MIWI, MILI (mouse homologue of PIWI proteins) regulate DNA cytosine methylation as well as heterochromatin formation in mouse male germline by similar mechanisms and are indispensable for process of spermatogenesis (Aravin et al., 2007b). In *C.elegans* germline both siRNAs (22G siRNAs) and piRNAs (21U RNAs) work together in a feedforward loop that ultimately recruits various histone methyltransferases (SET-25 and SET-32) and the HPL-2 silencing protein to initiate or maintain epigenetic memory against non-self RNA (Lee et al., 2012, Shirayama et al., 2012).

Unlike small ncRNAs, many of the larger ncRNAs share a biogenesis pathway similar to protein-coding messenger RNAs, including polyadenylation or splicing, and there is no defining biochemical feature that can be exclusively ascribed to them (Muers, 2011). Furthermore, recent studies have revealed an unexpected abundance, genomic complexity and transcriptional dynamics of long ncRNAs. For example, more than 50% of all mammalian protein coding genes appear to be associated with complementary non-coding transcripts that are either overlapping, intronic or bidirectional (Rinn and Chang, 2012) (Carninci et al., 2005). These and other long ncRNAs are likely to fulfill a plethora of hitherto poorly characterized cellular functions, based on their rich varieties in RNA structure, chemistry and presence of various modular domains associated with protein-, or RNA- and DNA binding (Washietl et al., 2012). For example, in embryonic stem cells, over 226 long ncRNAs regulate gene expression (both in *cis* and *trans*) as well as pluripotency and repression of lineage-specific states (Guttman et al., 2011). Furthermore, several ncRNAs bind to repressive chromatin remodeling complexes such as *Polycomb 2* (PRC2) complex which is associated with methylation of the histone H3-lysine 27 mark, and KMT1E/ESET methyltransferase complex for histone H3K9 methylation, and the JARID1C histone H3K4 demethylase complex (Guttman et al., 2011). The long ncRNA *Kcnq1ot1* recruits multiple chromatin remodeling complexes including PRC2 for H3K27 methylation and G9a for H3K9 methylation (Pandey et al., 2008). Similarly, the RNA *HOTAIR* is thought to maintain repressive states via binding to two different chromatin complexes, PRC2 at its 5' end and lysine-specific demethylase 1 (LSD1) at the 3' end (Tsai et al., 2010). The ncRNA, *CDKN2B-AS1/ANRIL*, which functions as a tumor suppressor gene and is downregulated in some types of cancers, binds the Suz12 subunit of the PRC2 complex as

well as chromodomain of CBX7 in the Polycomb 1 complex to trimethylate H3K27, which then mediates repression of the *CDKN2A/CDKN2B*, a locus commonly associated with the regulation of cell cycle and risk for various malignancies (Yap et al., 2010, Yap and Zhou, 2010, Tano and Akimitsu, 2012). Similarly, the long ncRNA P21 binds to PRC2 and ribonucleoprotein K (hnRNP-K) to create p53 dependent global repression of transcription in response to DNA damage (Huarte et al., 2010). Finally, some of the longer ncRNA exhibit complex regulatory scaffolds that are thought to function either in the context of activation or repression of gene expression (Tsai et al., 2010).

As the short list of above examples illustrates, there is a diverse and rapidly expanding array of molecular mechanisms by which the long ncRNAs could affect transcription. These mechanisms can be divided into the following types (Maston et al., 2012): (1) long ncRNA species that either facilitate or block gene expression by regulating genomic localization of transcription factors or repressive chromatin modifiers and remodeling complexes (Tsai et al., 2010, Guttman et al., 2011). (2) the long ncRNA is a mere byproduct of a regulatory mechanism in which the act of transcription itself is key to activate a cis-associated gene promoter (Abarrategui and Krangel, 2007, Lefevre et al., 2008). (3) Some chromatin-associated RNAs, including *Intergenic 10*, seem to populate numerous positions throughout the genome (Mondal et al., 2010), and may be an important structural part of chromatin, a view that is further supported by the finding that polyA⁺ RNA contributes up to 2–3% of the total nucleic acid content bound in chromatin (Rodriguez-Campos and Azorin, 2007).

Examples of ncRNAs implicated in the neurobiology and treatment of psychiatric disease

It is very likely that the different types of chromatin regulatory mechanism involving ncRNAs, as discussed above, are highly relevant for neuronal function in health and various disease states. In the following, we discuss a few specific examples of ncRNAs that are relevant from the viewpoint of psychiatric disease.

Bdnf antisense transcript

Brain-derived neurotrophic factor is a key regulator for growth and plasticity in the nervous system and implicated in the neurobiology of a wide range of brain disorders, ranging from various degenerative conditions to mood and psychosis spectrum disorders (Duman and Monteggia, 2006, Krishnan and Nestler, 2010, Nagahara and Tuszynski, 2011) and substance abuse and dependence (Horger et al., 1999, Akbarian et al., 2002). Importantly, developmental regulation of *BDNF* expression in the human prefrontal cortex involves a complex interplay of epigenetic factors as evidenced by an increase in open chromatin-associated H3K4 (tri)methylation (H3K4me3) at multiple *BDNF* gene promoters during the transition from the fetal period to child- and young adulthood (Mellios et al., 2008). During the subsequent periods of maturation and aging, small RNAs and microRNA-mediated posttranscriptional mechanisms play a more prominent role for the fine-tuning of BDNF expression (Mellios et al., 2008). Recently, it was discovered that a cis-acting *Bdnf* antisense transcript (*Bdnf-AS*) downregulates Bdnf expression in conjunction with increased, PRC2-mediated repressive chromatin remodeling and trimethylation of H3K27 (Modarresi et al., 2012). Importantly, single-stranded oligonucleotides and siRNA-mediated depletion of *Bdnf-AS* in adult mouse brain resulted in decreased epigenetic repression at the *Bdnf* locus (Figure 1A), in conjunction with a several-fold increase in *Bdnf* transcript and robust upregulation of BDNF protein in hippocampus and frontal cortex (Modarresi et al., 2012). Therefore, pharmacological approaches targeting growth factor-related antisense transcripts deserve further study in preclinical model systems of neurological and psychiatric disease and could complement new types of drug treatments aimed at shifting the balance between

open- and repressive chromatin-associated histone methylation and acetylation in the brain (Peter and Akbarian, 2011).

Human-specific non-coding RNA LOC389023

The above mentioned *Bdnf*-antisense transcript, *Bdnf*-AS is certainly not the only example of an ncRNA associated with epigenetic regulation important in the context of psychiatric disease. One interesting case in point is the 744bp long ncRNA, *LOC389023*, positioned in chromosome 2q14.1, within the gene body of *DPP10*. The *DPP10* gene encodes a dipeptidyl peptidase-related protein regulating voltage-dependent potassium channels that control neuronal excitability, membrane repolarization and repetitive firing, back propagation of action potential into dendrites, and dendritic integration and plasticity (Jerng et al., 2005, Zagha et al., 2005, Li et al., 2006, Maffie and Rudy, 2008, Maffie et al., 2013). Interestingly, rare structural variants of *DPP10* confer strong genetic susceptibility to autism (Girirajan et al., 2013) and asthma (Torgerson et al., 2012), while some of the gene's more common variants contribute to a significant risk for bipolar disorder, schizophrenia and asthma (Allen et al., 2003, Marshall et al., 2008, Djurovic et al., 2010, Michel et al., 2010). Furthermore, treatment with mood-stabilizing drugs, including lithium and valproate, increases *Dpp10* expression in the hippocampus probably by a post-transcriptional, microRNA-mediated mechanism (Zhou et al., 2009). Of note, histone methylation at the *DPP10* is regulated in cell type-specific manner, with levels of (open chromatin associated) H3K4me3 much stronger in cortical neurons than in non-neuronal cells and tissues (Shulha et al., 2012b). Furthermore, multiple H3K4me3 peaks at *DPP10*/Chr. 2q14.1 showed histone methylation enrichments that were unique to human cortical neurons, as compared to the non-human primate brain (Shulha et al., 2012b). These human-specific H3K4me3 enrichments are associated with the emergence of a novel RNA transcript, *LOC389023*, transcribed from within the *DPP10* gene body but in antisense (Shulha et al., 2012b). Strikingly, *LOC389023* harbors a GC-rich stem loop motif implicated in transcriptional repression by binding to TSS chromatin and recruitment of components of Polycomb PRC2 complex (Zhao et al., 2008, Kanhere et al., 2010). Consistent with this, *LOC389023* is bound both to chromatin and to SUZ12 (Shulha et al., 2012b), a zinc finger protein and core component of PRC2 that interact with the GC stem loop motif (Kanhere et al., 2010). In contrast, EZH2, a (H3K27) methyltransferase and catalytic component of PRC2, did not interact with *LOC389023*, consistent with previous reports on other RNA species carrying a similar stem loop motif (Kanhere et al., 2010). Therefore, *LOC389023/DPP10* (Figure 1B) emerges as a fascinating example for a novel, human-specific ncRNA recruiting repressive chromatin remodelers in *cis*, which then leads to decreased expression of the aforementioned *DPP10*. In situ hybridization studies showed that *LOC389023* is expressed in a subpopulation of neurons residing in the external cortical layers II–IV (Shulha et al., 2012b), which would suggest that this subset of neurons exhibit a very different signaling capacity than their counterparts in the non-human primate brain. Additional work is required to explore whether and how *LOC389023* may contribute to the emergence of cognitive abilities and disease vulnerability unique to human. Furthermore, it will be extremely interesting to explore whether human-specific ncRNAs other than *LOC389023* affect epigenetic regulation of neuronal or glial genes (Tolosa et al., 2008, Konopka et al., 2012, Zeng et al., 2012, Lipovich et al., 2013, Somel et al., 2013).

Multiple layers of epigenetic regulation at chromosome 15q11-13

Perhaps one of the most illustrative and complex examples as it pertains to molecular mechanisms governing epigenetic regulation in the nervous system involves chromosome 15q11-13, a highly regulated locus subject to genomic imprinting (parent-of-origin-specific gene expression) and responsible for a range of neurodevelopmental syndromes, including

Prader-Willi and Angelman, as well as for a subset of cases diagnosed with autism (Leung et al., 2011). DNA structural variants within this locus could contribute to genetic risk to schizophrenia, bipolar disorder and other psychiatric diseases (Leung et al., 2011). Of note, a very large ncRNA arises from *15q11-13*, covering 1Mb in the mouse and 600kb in humans and 148 exons and introns (Le Meur et al., 2005). This long *SNPRN-UBE3A* ncRNA, which normally is highly expressed on the paternal but not on the maternal chromosome, includes clusters of smaller non-coding RNAs that are thought to modulate nucleolar functions in neurons, and an antisense transcript, *UBE3A-AS* which suppresses *UBE3A* sense transcription of the same gene on the paternal chromosome (Leung et al., 2011). It has been suggested that the *SNPRN-UBE3A* ncRNA, and the smaller RNAs derived from it, produce a 'RNA cloud' in *cis*, which contributes to lasting decondensation of this locus on the paternal chromosome, including epigenetic decoration with open chromatin-bound histone modifications and loss of repressive chromatin-associated histone and DNA methylation (Xin et al., 2001, Leung et al., 2011). Strikingly, *UBE3A* (also known as E6-AP) encodes a ubiquitin ligase that targets RING-1B, a component of Polycomb repressive complex PRC1, for its subsequent degradation (Zaaroor-Regev et al., 2010). Therefore, dysregulated expression of long *SNPRN-UBE3A* ncRNA in the context of 15q11-13 imprinting disorders and/or genetic mutations and polymorphisms, may affect orderly activity of the PRC1 complex in developing brain (Tarabykin et al., 2000, Vogel et al., 2006, Golden and Dasen, 2012), with widespread implications for neuronal health and function.

Synopsis and Outlook

According to recent estimates by the GENCODE consortium, there are up 15,000 long (> 200bp) ncRNAs encoded in the human genome, and there could be an even larger number of smaller RNA species (Derrien et al., 2012, Harrow et al., 2012). A subset of long ncRNA were recently identified as important regulators of pluripotency and neurogenesis (Ng et al., 2012). Furthermore, some long ncRNAs, including *RP11-586K2.1* on chromosome 8, map to genetic susceptibility loci for common psychiatric disorders, including schizophrenia and bipolar disorder (Lin et al., 2011). It is likely that many of long ncRNAs, in addition to the *Bdnf-AS*, *LOC389023* and *SNRPN-UBE3A* examples discussed here, plus many smaller RNAs, will be of pivotal importance for orderly function of the developing and mature nervous system by interacting with chromatin remodeling complexes including PRC1 and PRC2. Both these Polycomb complexes are associated with a rapidly expanding cache of CBRs (Mondal et al., 2010). Given recent technological advances in the field, including the ChIRP technique (Chromatin Isolation by RNA Purification), which captures crosslinked RNA-protein-DNA complexes and in conjunction with tiling oligonucleotides designed to retrieve specific long ncRNA allows for rapid, genome-scale mapping of binding patterns of these ncRNAs (Chu et al., 2011), we foresee that the expanding universe of non-coding RNAs will soon contribute to important novel insights into normal brain function, and provide valuable leads towards novel treatments of psychiatric disorders.

Acknowledgments

Work in the authors laboratory is supported by the research awards from the National Institutes of Health.

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Highlights

- Provides an update on the evolving knowledge of non-coding RNA in the genome
- Discusses the different types of epigenetic regulations by non-coding RNA
- Highlights chromatin-associated RNA important for psychiatric disease

Figure 1. Long ncRNA-mediated epigenetic fine tuning of neuronal transcript

(A, B) Hypothetical examples of Polycomb PRC2 mediated repressive chromatin remodeling. (A) At the *BDNF* gene locus (chromosome 11p13/14.1), two separate promoters are thought to drive expression of *BDNF* sense and antisense transcript. Studies in mouse (Modarresi et al., 2012) confirm that the natural antisense transcript is a negative regulator for *BDNF* expression and neurotrophic function. These mechanism may involve repressive PRC2 chromatin remodeling at the *BDNF/Bdnf* locus, and removal of the antisense *Bdnf-AS* by short interfering RNAs (that trigger degradation by the RISC-Argonaute 2 pathway) decreases levels of the repressive histone mark, trimethyl H3K27. (B) A different type of chromatin-associated regulatory mechanism involving PRC2 and ncRNA may operate at the *DPP10* locus on chromosome 2q14.1, which is defined by the emergence of a human-specific long ncRNA, *LOC389023* in conjunction with increased enrichment for open chromatin-associated trimethyl H3K4 (H3K4me3) (Shulha et al., 2012b). The *LOC389023* transcript, via a GC-rich stem loop motif, is thought to recruit components of the PRC2 complex, including the SUZ12 zinc finger repressor protein. These mechanisms could then contribute to the observed human-specific downregulation of *DPP10* transcript in the prefrontal cortex (Shulha et al., 2012b). Additional work is required in order to clarify whether SUZ12 acts by recruiting additional PRC2-associated proteins to the *DPP10* locus, and whether there is increased repressive histone methylation (H3K27me3) at *DPP10*.