

Stress, chromatin, and long noncoding RNA: A new frontier in psychiatric biology

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Long noncoding RNAs (lncRNAs) are lengthy RNA molecules (more than 200 nucleotides) that are not translated into proteins. These molecules are precise regulators of gene action, activating or silencing genes and influencing the chromatin structure that packages DNA in the nucleus. In this way, lncRNAs contribute to the upregulation or suppression of genes that activate, develop, or adapt the neuronal signalling apparatus in response to cellular stress (1).

Stress, glucocorticoid receptor, and lncRNAs

Stress causes long-term changes in brain structure and function, representing a significant risk factor for psychiatric illnesses such as major depressive disorder (2). While most studies have focused on neurotransmitters and synaptic activity, the work by Verma, Roy, and Dwivedi, the cover article in this issue of *Genomic Psychiatry*, takes a genomic perspective that offers fresh insights into stress pathophysiology. The authors' proposal that stress-induced chromatin remodeling by lncRNAs provides the framework for enduring neural changes involving the glucocorticoid receptor is both compelling and timely.

The glucocorticoid receptor operates in neural cells when activated by stress hormones, promoting important changes in lncRNA activity and transcriptional regulation (3, 4). This receptor functions as a master regulator of cellular stress responses, and its prolonged activation under chronic stress conditions can trigger maladaptive molecular cascades. By examining how glucocorticoid receptor activation influences lncRNA expression and subsequent chromatin modifications, this work illuminates a critical mechanism linking environmental stress to persistent changes in gene expression patterns.

Key findings and mechanistic insight

Verma et al. (1) simulated chronic stress in cultured SH-SY5Y cells by continuous stimulation of the glucocorticoid receptor. The transcriptome examination of lncRNAs revealed that 79 lncRNAs were significantly changed, of which 44 were overexpressed while 35 were downregulated. The distribution pattern of lncRNAs on chromosomes is also different. For example, chr1 and chr15 are enriched for downregulated lncRNAs, while chr11 and chr12 are enriched for upregulated lncRNAs, suggesting coordinated genomic responses. This chromosome-wide distribution suggests the stress-inducible lncRNAs may not simply function as regulatory elements, but are involved in regulation at a higher organizational level.

Additionally, the differentially expressed lncRNAs displayed diverse RNA biotypes, including intergenic, antisense, and sense-overlapping, which presumably utilise different mechanisms for gene regulation. According to network analysis, specific lncRNAs act as master regulators of gene clusters that control neuronal survival, synaptic transmission, and calcium homeostasis. These processes are critical for normal neuronal function and become disrupted in stress-related psychiatric disorders (5).

According to the study, lncRNAs interact physically with certain molecules, and this is critical to understanding the mechanism. Furthermore, these molecules work with a chromatin remodeling complex. This complex is called PRC2 (polycomb repressive complex 2). According to

RNA immunoprecipitation (RIP) assays, 51 lncRNAs bound to the EZH2 subunit, the catalytic component of PRC2 (polycomb repressive complex 2); 87 lncRNAs also pulled down with the H3K27me3 mark, a canonical transcriptional repression mark. Communication between the PRC2 complex and chromatin occurs via the CXC and DNA-binding proteins. Through these interactions, PRC2 is brought to specific loci on specific chromosomes, where it deposits H3K27me3 and silences those genes. It also converts already accessible euchromatin to repressive heterochromatin.

According to Verma et al., lncRNAs function as scaffolds to recruit PRC2-mediated chromatin silencing to clusters of neuronal signalling and training-essential protein-coding genes (6). Three "star" lncRNAs (ENSG00000225963.8, ENSG00000228412.9, and ENSG00000254211.6) were consistently activated by the glucocorticoid receptor and enriched in EZH2 and H3K27me3 RIPs, providing consistent hits mechanistically for this silencing pathway. The lncRNAs identified in their study represent high-priority candidates for future functional studies of stress-induced transcriptional repression.

By integrating lncRNA expression data with transcriptomic data, we observe that stress-responsive lncRNAs show an inverse correlation with the expression of nearby genes. This finding supports a model where lncRNAs guide local gene repression by modifying chromatin. Gene ontology analysis of the upregulated genes revealed the processes related to synapse function, neurotransmitter receptor activity, and neuronal signaling. Disruption of these biological processes has been repeatedly associated with depression and other stress-related disorders. Findings indicate that lncRNA-PRC2 complex binding is responsible for silencing mood-related genes and provides a mechanistic link between stress exposure and the transcriptional changes observed in mental illness.

Strengths of the study

Verma et al. present an interesting study that employs transcriptomics, RNA immunoprecipitation, and network analysis to provide a broad view of gene expression under chronic stress (1). The study uses a multi-layered experimental approach, with lncRNA profiling, chromatin immunoprecipitation, and mRNA expression studies providing converging evidence for the proposed mechanism.

This method of combining things is a big step forward over studies that examine only one level of regulation.

The study's assessment of lncRNA activity across genomic and functional annotations provides valuable new insight into the molecular processes of psychiatric disease. The authors provide a molecular cartography of the stress-responsive regulatory elements by mapping lncRNA to chromosomal locations and biotyping them. Finding a clear link between lncRNA biotypes and PRC2 activity is a big step in understanding the epigenetic basis of major depression.

Moreover, direct physical evidence of lncRNA-protein interactions can be obtained by RNA immunoprecipitation-sequencing rather than relying solely on correlative data. The technical rigor increases confidence of the mechanistic conclusions and establishes a method for future studies in this field.





Glucocorticoid receptor-mediated lncRNA regulation in major depressive disorder

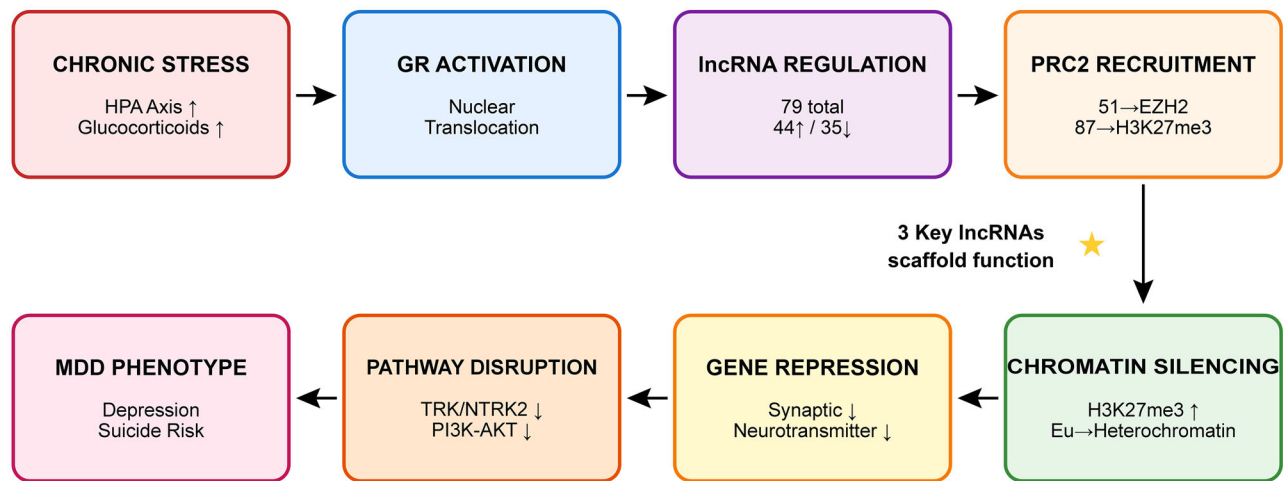


Figure 1. Molecular pathway linking chronic stress to major depressive disorder through lncRNA-mediated chromatin silencing. Chronic stress activates the HPA axis, elevating glucocorticoid levels and triggering nuclear translocation of the glucocorticoid receptor (GR). GR activation regulates 79 lncRNAs (44 upregulated, 35 downregulated). Three key lncRNAs with scaffold function recruit Polycomb Repressive Complex 2 (PRC2), with 51 lncRNAs enriched in EZH2 pull-down and 87 enriched in H3K27me3 pull-down. This drives chromatin silencing through H3K27me3 deposition and euchromatin-to-heterochromatin transitions, leading to the repression of synaptic and neurotransmitter-related genes. Pathway disruption includes downregulation of NTRK2 and PI3K-AKT signaling, contributing to the MDD phenotype characterized by depression and suicide risk.

Limitations and future directions

Several limitations merit consideration. The study was conducted in a cellular model rather than in primary neural tissue or an animal model, which limits its applicability to human disease (7). Cell culture systems provide scientists with experimental control and enable them to dissect a specific molecular pathway at the mechanistic level. Despite this, cell culture systems may not faithfully mimic all stress responses in an intact brain, where different cell types interact within a well-organized neural circuit.

It is still unclear when these chromatin changes happen in different cell types. Neuron types may differ in their susceptibility to stress-induced changes in lncRNA, and the dynamic nature of these changes during stress and recovery warrants investigation. Using overexpression systems can provide insights into molecular mechanisms; however, these systems might not accurately reflect the subtle stress responses that occur in the body under physiological conditions.

Future research should employ a variety of other strategies. After death, the brain examines lncRNA expression and chromatin states in stress-sensitive regions of individuals with depression to establish clinical relevance. Using animal models of chronic stress could determine whether the same lncRNA-mediated chromatin changes happen in vivo, and whether they correlate with behavioural phenotypes. Advanced techniques could map genomic reorganization due to lncRNA-PRC2 activity. More research with patient-derived samples, animal models, and advanced chromatin mapping technologies would strengthen these findings and clarify their translational potential.

Conclusions

Despite its limitations, the work of Verma et al. was novel and a significant step forward in genomic psychiatry. It is possible that lncRNAs modulate stress-induced chromatin silencing, affecting gene networks involved in psychiatric function and providing insights into how an experience is translated into the genome via epigenetics. The observation that suppressed genes were enriched for psychiatric disease associations in the DisGeNET database, including suicide, mood disorders, and panic disorder, together with evidence of convergent synaptic dysregulation in major depressive disorder (MDD), gives clinical context to these molecular findings (8). It suggests that chromatin changes mediated by lncRNA may have a direct role in disease pathology.

Both research and action can be taken based on these findings. From a mechanistic perspective, we can now identify lncRNAs that mediate stress-induced gene repression, providing a molecular entry point for understanding how transient environmental exposures can create persistent neurobiological alterations. Stressful situations induce epigenetic modifications and are potentially reversible. Hence, this calls for therapies that can restore chromatin and gene expression patterns in brain tissue.

The findings of this study should inspire further investigation of lncRNA-mediated regulation in different psychiatric illness-related contexts. We will support future research on genomic, epigenomic, and clinical data integration to link underlying molecular mechanisms with clinical phenotypes. As the field progresses, technologies that enable manipulation of specific lncRNAs in the intact brain, together with detailed phenotyping, will be necessary to establish causal relationships and assess therapeutic potential. Verma et al.'s work is an important step toward a more complete molecular understanding of how stress contributes to psychiatric vulnerability, something that may ultimately inform more efficacious prevention and treatment of stress-related disorders.

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