Editorial

The long and short of it: long noncoding RNAs in neural development and diseases

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1. Versatile and stratified functionalities of lncRNAs

Long noncoding RNAs (lncRNAs) are emerging nucleic acid polymers that play key regulatory and structural roles in numerous cellular processes [1–3]. While the true gamut of their impressive functional repertoire still awaits full investigation, much is now known about some of their diverse nuclear and cytoplasmic functions. In the nucleus, lncRNAs can reshape chromosome architecture, modulate chromatin interactions and remodeling, regulate transcription initiation and elongation, etc. [4–10]. Notably, both the act of lncRNA biogenesis and the resulting transcripts can contribute to regulation [11, 12]. Interestingly, lncRNAs are also found to act as scaffolds to nucleate the formation of dynamic ribonucleoprotein assemblies termed nuclear bodies [13–15]. Although most lncRNAs are retained in the nucleus, some function in the cytoplasm and even mitochondria to rheostat mRNA stability and translation, through direct interactions with mRNAs, microRNAs, RNA-binding proteins, and even ribosomes [16–18]. Even post-translational modification such as phosphorylation can be controlled by lncRNAs by altering target protein interaction with kinases and phosphatases [19, 20].

Despite these fascinating biological effects, there exist significant barriers in the functional and mechanistic elucidations of lncRNAs. First, frequent gene redundancy in humans makes it difficult to assign function to individual lncRNA genes based on single-gene manipulations. This is exemplified by the case of *Drosophila roX1* and *roX2* genes and possibly also MALAT-1 (Metastasis Associated Lung Adenocarcinoma Transcript 1) genes [21–23]. Second, as lncRNA genes can function at various points of regulation and in distinct forms, it can be difficult to distinguish among the effects of the lncRNA transcripts *per se*, protein products some lncRNAs are now known to encode, and the act of their transcription and processing [10, 24]. Third, the primary sequences of most lncRNAs are not well conserved, and many of them are limited to mammalian genomes [25, 26]. This hampers effective multiple sequence alignments which are used to extract information about conserved regions and sequence motifs. Finally, at the levels of secondary and tertiary structures, many if not most lncRNAs exhibit limited sequence covariation that would support the presence of well-conserved stem regions, which are hallmarks of conserved functional structures found in known structured RNAs [25, 27, 28]. With the recent flourish and application of artificial intelligence and neural networks in biology, there may be opportunities to apply these emerging technologies in the analysis, classification, pattern search, and prediction of the secondary and tertiary structures of lncRNAs. If successful, these approaches may also provide another route towards establishing structure-function relationships.

2. Regulatory roles of lncRNAs in neural development and pathology

The versatile and stratified functionalities of lncRNAs are especially pronounced in the central nervous system (CNS), particularly in the brain. Many lncRNAs are expressed to much higher levels in the brain and some conserved lncRNAs appear to be brain-specific [29, 30]. These findings are in line with the notion that gene expression programs during CNS and brain development, compare to

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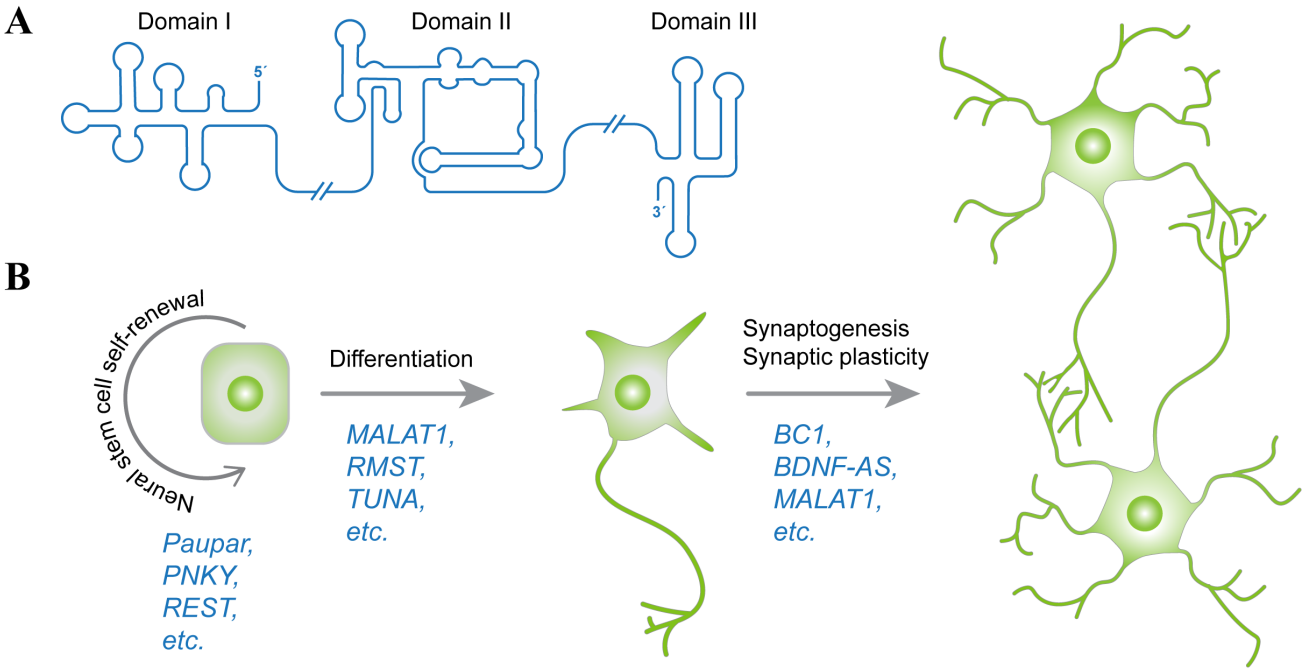

Fig. 1. A simplified view of regulatory lncRNA functions in neural development and pathology. (A) Multi-domain secondary structure of an envisioned lncRNA, featuring numerous hairpin stem loops, single-stranded regions, multi-helix junctions, compact domains harboring tertiary folds, long-range interactions such as pseudoknots, etc. (B) Diagram of neural development regulation by representative lncRNAs. Depicted are lncRNA-regulated developmental phases of neural stem cell self-renewal (left), commitment to differentiation (middle), and synaptogenesis and synaptic plasticity (right).

those of other tissues and organs, require more precise, sophisticated and coordinated control. However, as discussed above, the mechanistic analyses of lncRNAs in various biological contexts have been challenging, due to their low copy numbers, gene redundancy, general lack of significant sequence conservation and co-variation, and a paucity of structural information at secondary, tertiary and quaternary levels (Fig. 1A) [27, 31–33]. Indeed, high-resolution structural and mechanistic analyses of noncoding RNAs much smaller than most lncRNAs are already technically challenging, despite the recent resolution revolution brought by single-particle cryo-EM analyses [34–38]. These deficiencies have partially contributed to seemingly conflicting findings and models for the proposed mechanisms of action by some lncRNAs. Therefore, comparative meta-analyses that compare and contrast multiple lines of evidence to synthesize and derive general insights and trends are valuable, at this early developmental stage of lncRNA biology.

One such analysis, by Oe *et al.* [39], starts with the known roles of select lncRNAs in the course of neuronal differentiation, from the self-renewal of the neuronal stem cells, to commitment to cell fates, and to their functional maturation (Fig. 1B). Indeed, a great number of lncRNAs contribute to this initial phase of neural development, including MALAT1, TUNA (Tcl1 Upstream Neuron-Associated lincRNA), etc. [40, 41]. Once the neurons have differentiated and their characters assigned, dendrites and axons grow outward and make the first synapses to start forming neural circuits, in a process known as synaptogenesis. LncRNAs such as MALAT1, FMR4 (fragile X mental retardation 4) and BC1 (Brain cytoplasmic RNA 1) regulate synaptogenesis or synaptic plasticity [40, 42]. Synaptic plasticity is the final phase of neural development in which synaptic transmissions change strength or efficacy in response to stimuli, and is essential for brain functions including learning and memory. Interestingly, synaptic plasticity is suggested to also modulate the expression of a large set of lncRNAs, thus allowing for mutual regulation and potential feedback control [43].

Logically, deregulation of lncRNA expression and operation is linked to the onset and pathogenesis of a number of neurological diseases. Oe *et al.* [39], focuses on discussing known correlations between lncRNA deregulation and primary neurological diseases including neurodegenerative diseases such as Alzheimer's and Parkinson's diseases, and glioma, brain cancers of glial cells that surround and support neurons. Interestingly, the proposed mechanistic pathways connecting the implicated lncRNAs (e.g., HOTAIR, NEAT1, 51A) to the disease pathologies frequently involved direct lncRNA interactions with microRNAs, regulation of target mRNA and protein stability, as well as epigenetic regulation such as alteration of DNA methylation.

While the analysis of Oe *et al.* [39], highlights two decades of exciting progress at the crossroads between lncRNA biology and neural development and pathology, much remains to be affirmed and clarified, in order to trans-

late such basic knowledge to reliable diagnostics, therapies and clinical applications. What is also clear is that fundamental mechanistic analyses of lncRNAs at the molecular and structural level are needed to deepen our understanding of these newly adopted regulatory polymers, which frequently exhibit novel and often surprising modes of operation and unusual patterns of conservation [32, 44].

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5. Conflict of interest

The author declares no conflict of interest.

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