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ACCEPTED MANUSCRIPT

Long Noncoding RNAs: Central to Nervous System Development

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Summary

The development of the central nervous system (CNS) is a complex orchestration of stem cells, transcription factors, growth/differentiation factors, and epigenetic control. Noncoding RNAs have been identified, classified, and studied for their functional roles in many systems including the CNS. In particular, the class of long noncoding RNAs (lncRNAs) has generated both enthusiasm and skepticism due to the unexpected discovery, the diversity of mechanisms, and the lower level of expression than found in protein-coding RNAs. Here we describe evidence supporting the role of lncRNAs in driving CNS-specific differentiation. It is clear that lncRNAs exhibit a functional diversity that makes their study and compartmentalization more challenging than other classes of noncoding RNAs. We predict, however, that lncRNAs will be essential for the characterization of discrete neuronal cell types in the age of single-cell transcriptomics and that these regulatory RNAs contribute to the multitude of functional mechanisms during CNS differentiation that will rival the diversities of protein-based mechanisms.

An Introduction to Noncoding RNAs in CNS Development

Some of the more important distinguishing features of mammalian genomes are the complex mechanisms by which genes are regulated in coordinate fashion during development. This orchestration is most evident in the complexity, organization, and function of the mammalian brain. Here, the synchronized regulation by precise attenuation or activation of functional genetic components establishes a staggering variety of cell types, and, remarkably, enables the integration of these diverse cell types into the functional circuitry of the brain. A shared characteristic of many traumatic brain injuries or neurodegenerative disorders is a specific effect on discrete neuronal subtypes, demonstrating that individual neuronal subtype are likely to be metabolically distinct from each other. Certain neuronal subtypes may be acutely sensitive to disease progression by mechanisms such as enhanced sensitivity to oxidative stress (e.g. dopaminergic neurons in

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