Genomic Mechanisms of Protein-DNA Interactions during Nervous System Development

Ho Sung Rhee
Department of Cell & Systems Biology, University of Toronto, Mississauga, Ontario, L5L1C6, Canada

Abstract

Cell identity is established by cooperative binding between DNA-binding proteins, called transcription factors, and enhancer DNA during mammalian development. Enhancer DNA plays important regulatory roles in cell-type-specific gene expression. Many neural transcription factors are expressed only transiently during nervous system development in mammals. How expression of neural genes is maintained following downregulation of early neural transcription factors in maturing neurons remains unknown. Using a high-resolution genomic mapping method, called ChIP-exo, we show genome-wide mechanisms of how transcription factors control maintenance of neural gene expression. Next, we demonstrate how noncoding DNA regions, composing 98% of the mammalian genome, are organized to regulate cell-type-specific gene expression programs. Most noncoding DNA in mammals resides in intergenic DNA regions located between two neighboring genes. We reveal long intergenic DNA length-dependent neural gene expression patterns, reflecting the complexity of the mammalian nervous system. We also show that the intergenic regions of neural genes have many tissue-specific active enhancers containing distinct transcription factor binding sites. Our results suggest that noncoding DNA architecture is not random but instead is uniquely organized in the mammalian nervous system.