CSB DEPARTMENTAL SEMINAR

Enhancers are genes

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There are hundreds of thousands of highly alternatively spliced long noncoding RNAs (lncRNAs) expressed from the human genome. There are hundreds of publications describing the involvement of lncRNAs in various developmental, neurological and disease processes, including our recent work showing that a lncRNA is required for hippocampal but not cortical memory and another for spatial navigation in females. However, a conceptual framework for understanding lncRNA evolution and function is lacking. Synthesizing the evidential landscape, it appears that most lncRNAs are the products of genetic loci called enhancers, which control the spatiotemporal patterns of development, estimated to number hundreds of thousands, perhaps well over a million, in the human genome. A widely accepted model proposed in the 1980s posited that enhancers function as binding sites for transcription factors that loop to contact promoters of target genes, but it has since emerged that enhancers are transcribed in the cells in which they are active to produce (like protein-coding genes) both short bidirectional transcripts and long multi-exonic RNAs. A variety of studies have shown that enhancer-derived lncRNAs (elncRNAs) are required for enhancer function and that alternative splicing of elncRNAs alters enhancer action. The emerging picture is that elncRNAs scaffold topologically associated phase-separated chromatin domains by interaction with histone modifiers, transcription factors and other proteins containing intrinsically disordered regions (IDRs) and guide these proteins to target genes by RNA-DNA interactions. The recognition that enhancers are genes explains the g-value enigma, the cell-specific expression and rapid evolution of lncRNAs under positive selection for adaptive radiation, and the genome-wide incidence of transcription start sites, splice sites and epigenetic modifications documented by the ENCODE project. Moreover, the extensive alternative splicing of lncRNAs and posttranslational modifications of the IDRs in proteins required for developmental processes provides a framework for understanding the numbers and features of the majority of lncRNAs and how trillions of cell fate decisions are made accurately during human ontogeny. The next challenge is to decipher the structure-function relationships in lncRNAs.

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