Abstract

Temporal and spatial regulation of the Caenorhabditis elegans lin-4 microRNA gene

By

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Development is a stepwise process that is controlled by gene regulatory networks (GRNs) that generate sequential patterns of cell divisions and execute these programs at the appropriate times. In Caenorhabditis elegans (C. elegans), development progresses through four larval stages (L1-L4) where stage-specific patterns of cell division and cell fate are established in order. Transitions between patterns of development are mediated by the sequential expression of multiple microRNAs (miRNAs) that function in dosage-dependent fashions as “molecular switches” to repress the expression of temporal selector genes.

We show that the dosage of C. elegans miRNA lin-4 is controlled, temporally and spatially, through a combinatorial mechanism involving shadow enhancers and repetitive transcriptional cycles. More specifically, we show that these shadow enhancers regulate the amplitude of expression in a spatially restricted manner directly through modulating the duration of the transcriptional period. Through analysis of transcriptional patterns and modeling of expression dynamics of lin-4 miRNAs, we suggest that lin-4 functions across development to regulate the sequential down-regulation of multiple developmental targets in a manner analogous to the function of morphogens that control spatial gene regulation. Like the spatial gradients establishing body plan in Drosophila development, lin-4 establishes a temporal gradient to set the temporal plan of C. elegans development. It is likely that different transcription factors function through the enhancer elements to establish this temporal gradient in a tissue specific manner and that each larval stage contains different targets for lin-4.