Topology and Dynamics of the Zebrafish Segmentation Clock Core Circuit

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The segmented pattern of the vertebral column, one of the defining features of the vertebrate body, is established during embryogenesis. The embryo's segments, called somites, form sequentially and rhythmically from head to tail. The periodicity of somite formation is regulated by the segmentation clock, a genetic oscillator that ticks in the posterior-most embryonic tissue: for each tick of the clock, one new bilateral pair of segments is made. The period of the clock appears to determine the number and the length of segments, but what controls this periodicity? In this contribution[1], we have investigated the interactions of three transcription factors that form the core of the clock's regulatory circuit, and have measured how the period of segmentation changes when these factors are mutated alone or in combination. We find that these three factors contribute to a "dimer cloud" that contains all possible dimeric complexes formed from monomeric protein molecules; however, only two dimers in this cloud can bind DNA, which allows them to directly regulate the oscillatory gene expression that underpins the periodicity of segment formation. Nevertheless, a mathematical model of the clock's dynamics based on our experimental findings (see Fig. 1) indicates that the non-DNA-binding dimers also influence the stability, and hence the function, of the two DNA-binding dimers controlling the segmentation clock's period. Such involvement of non-DNA-binding dimers is a novel regulatory principle for the segmentation clock, which might also be a general mechanism that operates in other biological clocks.

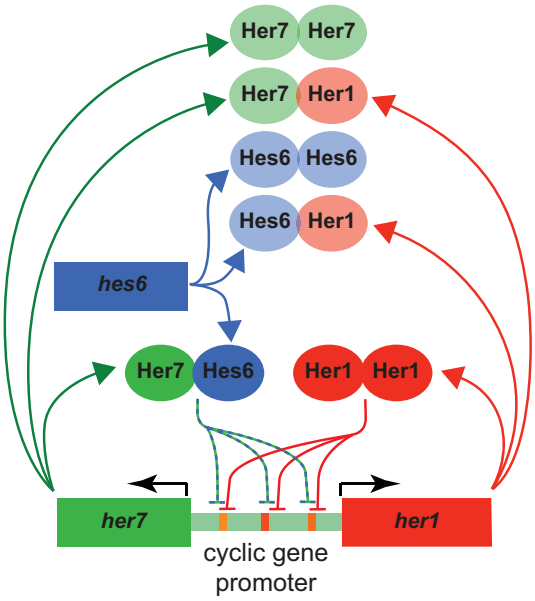

FIG. 1. Schematic representation of experimentally determined protein-protein interactions and protein-DNA interactions, neglecting weak protein-DNA interactions. Proteins are represented as ovals and genes by rectangular boxes. Blunted arrows represent repression of her1 and her7 promoters by Her1 homodimers and Her7:Hes6 heterodimers. Colored arrows represent production.

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