Hes7, a Negative Feedback Regulator of Notch Signaling, is Essential For Morphogenetic Robustness

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Abstract:

Developmental system is expected to be robust despite environmental fluctuations or internal noise. During embryonic development, *Hes7*, negative feedback regulator of Notch signaling, orchestrates the temporal and spatial aspects of somite formation and axial skeleton development. However, the developmental consequences of *Hes7* haploinsufficiency, characterized by the existence of a single functioning allele, remain unclear. This study aims to investigate the impact of *Hes7* heterozygosity on the robustness of somitogenesis and axial skeletal development. Fluorescence *in situ* hybridization (FISH) was conducted at the somite level where no significant differences were noticed regarding the expression of *Uncx4.1*, a posterior somite marker, between WT and *Hes7*$^{+/-}$ embryos, suggesting preserved anterior-posterior (A/P) somite polarity under normal condition. However, significant transcriptional fluctuation of *Hes7* was observed between WT and *Hes7*$^{+/-}$ embryos at the PSM. To investigate the effects of this transcriptional fluctuation, I administered valproic acid (VPA), a known external perturbation, intraperitoneally and found minor skeletal defects in WT neonates whereas *Hes7*$^{+/-}$ neonates showed severe skeletal abnormalities. At the embryonic stage, more abnormal somites were observed in *Hes7*$^{+/-}$ embryos compared to WT following VPA treatment. These findings support the hypothesis that one allele missing of *Hes7* compromises the robustness of the segmentation clock, rendering somitogenesis more vulnerable to environmental perturbations.