A HOX complex, a repressor element and a 50 bp sequence confer regional specificity to a DPP-responsive enhancer

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A central theme during development and homeostasis is the generation of cell type-specific responses to the action of a limited number of extant signaling cascades triggered by extracellular ligands. The molecular mechanisms by which information from such signals are integrated in responding cells in a cell-type specific manner remain poorly understood. We have undertaken a detailed characterization of an enhancer that is regulated by DPP signaling and by the homeotic protein Labial and its partners, Extradenticle and Homothorax. The expression driven by this enhancer (lab550) and numerous deletions and point mutants thereof was studied in wild-type and mutant Drosophila embryos as well as in cultured cells. We find that the lab550 enhancer is composed of two elements, a Homeotic Response Element (HOMRE) and a DPP Response Element (DPPRE) that synergize. None of these two elements can reproduce the expression of lab550, either with regard to expression level or with regard to spatial restriction. The isolated DPPRE of lab550 responds extremely weakly to DPP. Interestingly, we found that the inducibility of this DPPRE is weak because it is tuned down by the action of a repressor element. This repressor element and an additional 50 bp element appear to be crucial for the cooperation of the HOMRE and the DPPRE, and might tightly link the DPP response to the homeotic input. The cooperation between the different elements of the enhancer leads to the segmentally restricted activity of lab550 in the endoderm and provides a mechanism to create specific responses to DPP signaling with the help of a HOX protein complex.

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