A conserved cluster of homeodomain binding sites in the mouse Hoxa-4 intron functions in Drosophila embryos as an enhancer that is directly regulated by Ultrabithorax

JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

ID 152878
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Year 1997
Title A conserved cluster of homeodomain binding sites in the mouse Hoxa-4 intron functions in Drosophila embryos as an enhancer that is directly regulated by Ultrabithorax
Journal Developmental biology
Volume 186
Number 1
Pages / **Article-Number** 1-15
Keywords Animals; Base Sequence; Binding Sites/physiology; *Conserved Sequence; DNA Primers/chemistry; DNA-Binding Proteins/*metabolism; Drosophila/*embryology; *Drosophila Proteins; Female; Gene Expression Regulation; Developmental/genetics; Genes; Homeobox/*genetics; Homeodomain Proteins/*metabolism/*physi Introns/*physiology; Male; Mice; Molecular Sequence Data; Trans-Activators/*physiology; *Transcription Factors

The evolutionary conservation of the homeodomains suggests that their in vivo DNA binding sites may also be conserved between vertebrates and invertebrates. The regulatory function of the mouse Hoxa-4 and Hoxb-4 introns were analyzed in Drosophila since they both contain a cluster of three homeodomain binding sites, the HB1 element, which was also found in the introns of other Hox genes ranging from fish to humans as well as in the Ultrabithorax (Ubx) and decapentaplegic (dpp) genes of Drosophila. The enhancer of the Hoxa-4 intron was found to respond to several homeobox genes activating a lacZ reporter gene in particular cells of the epidermis in Drosophila embryos. The enhancer activity was found to be similar to previously described autoregulatory elements of Deformed (Dfd), the Drosophila homolog of Hoxa-4, but additional expression was observed in more posterior segments activated by Ubx and repressed by abdominal-A (abd-A). Point mutations in the homeodomain binding sites in HB1 abolished the enhancer activity. A second site suppression experiment showed that UBX interacts directly with the HB1 element. When the HB1 element in the Hoxa-4 intron was replaced by that of the mesodermal enhancer of dpp, which was previously shown to be directly controlled by Ubx, Ubx-dependent activation was retained, but repression by abd-A was lost. The same result was obtained when the third binding site of HB1 was altered, suggesting that this site is responsible for abd-A-dependent repression. Finally, deletion of potential cofactor binding sites flanking the HB1 element that are also conserved in the medaka, chicken, and mouse genes revealed that they are important for enhancer function in Drosophila and that the Dfd-dependent and the Ubx-dependent expression requires different sites. The evolutionary and functional conservation of the HB1 elements indicates that not only the homeodomains but also some of their in vivo binding sites are conserved between vertebrates and invertebrates.

Publisher Academic Press
ISSN/ISBN 1095-564X
edoc-URL http://edoc.unibas.ch/dok/A5257304
Full Text on edoc No;
Digital Object Identifier DOI 10.1006/dbio.1997.8582

PubMed ID http://www.ncbi.nlm.nih.gov/pubmed/9188748
ISI-Number WOS:A1997XE32200001
Document type (ISI) Journal Article