

Target genes and mode of action of transcription factors

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Research Field and Subjects

The Hox proteins are transcription factors playing key roles during animal development as well as for specific differentiation pathways at adulthood. Typically in vertebrates, these transcription factors are involved in the patterning of the main body axis, including the vertebral column and the central nervous system. Gene inactivation strategies allowed to extensively document the roles of the homeotic (Hox) genes. However, little is known about the mode of action of these transcription factors, and in particular, about the target genes under their control. In our research group, two kinds of approaches are pursued to unravel the mode of action of two Hox proteins, Hoxa1 and Hoxa2.

1. Target genes of homeotic proteins.

A first approach consists in elaborating cellular model systems in which the forced and/or inducible expression of a Hox protein (and its transcriptional cofactors) allows the identification of target genes through the differential analysis of the mRNA content of treated and untreated cells. Several cellular models have been designed, among which some specifically allow to fish out genes falling under the direct control of the transcription factor under analysis.

The use of these models allowed to identify large sets of target genes for Hoxa2. To further analyze the roles of these targets, and to correlate them to the function of Hoxa2, expression patterns are studied at different stages of mouse embryonic development. Gene inactivation strategies will be initiated to unravel the function of the most interesting targets, in regard to their involvement in the cellular and molecular pathways under the control of Hoxa2.

Similarly, the use of such models allowed the refined analysis of the regulatory cues at work in the specific control of targets: mapping enhancers of transcription, identification of cis-acting regulatory sequences and of trans-acting factors stimulating or inhibiting gene expression.

2. Mouse models for the developmental roles of Hox proteins. For the *in vivo* investigation of the mode of action of Hoxa1 and Hoxa2, we generated two kinds of transgenic mice.

Replacing the wild type allele of a Hox gene by mutated alleles coding for proteins with targeted amino acid substitutions allowed to address the structure-function relationship of protein domains *in vivo*. For example, we generated such “knock-in” mice for which the mutated allele introduced to replace the Hoxa1 gene codes for a protein that has lost the ability to recruit specific transcriptional cofactors. The subsequent analysis of mutant mice revealed the crucial importance of such protein-protein interactions *in vivo*. In fact, the mutant mice harboring the Hoxa1 point mutation displayed developmental abnormalities reminiscent of those caused by the full inactivation of the gene.

Adding genetically engineered versions of a Hox gene to lead to a gain of function, allows to investigate which specific cellular processes are under the control or may be misregulated by a Hox protein. Misexpression of a Hox protein in specific tissues like cartilages or blood vessels led to developmental defects whose ongoing analysis is relevant to the function normally fulfilled by the transcription factor.

Products and Services

- ▶ Transgenic Mouse lines
- ▶ Cell lines relevant for gene induction
- ▶ Expertise in mouse transgenesis

Representative References

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Partnership

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