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Abstracts

Functional Genomics

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Cis-regulatory organization of the Dll-B gene in *Ciona intestinalis*

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The Dll-B gene in the ascidian *Ciona intestinalis* is a member of a 2-gene convergently transcribed cluster, similar to the Dlx clusters of vertebrates. Comparative sequence analysis reveals several conserved sequences upstream of Dll-B and one in the intergenic region between the two genes, which may be *cis*-regulatory elements. In vertebrates, the intergenic *cis*-regulatory elements of the Dlx clusters are major activators of transcription of flanking genes. However, in *C. intestinalis*, tests of reporter transgenes incorporating different segments of the cluster indicate that the major activators of Dll-B are located upstream of the transcription start site. This suggest that although the basic structure of the Dlx cluster in *C. intestinalis* is similar to that of the vertebrate clusters, the *cis*-regulatory organization differs significantly.

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A tale of two morphogen gradients: Identifying Gli targets of Hedgehog Signaling

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The Hedgehog (Hh) signaling pathway acts as a morphogen to mediate digit patterning in the limb bud and specification of ventral neuronal cell types in the developing CNS. At the transcriptional level, the Hh pathway is mediated by the Gli proteins (Gli1–3), but little is known about the direct targets of these transcriptional effectors. In an approach to identify direct targets of Gli regulation in the developing nervous system, we developed a genetic system that relies on inducible, tagged Gli constructs to recover targets through Gli binding. We then performed chromatin immunoprecipitation (ChIP) on neuralized embryoid bodies containing the tagged Gli knock-in constructs and used the product to probe high density custom genomic arrays (60 kb of tiled sequence per locus). These experiments identified all four of the currently characterized Gli binding *cis*-regulatory regions of genes known to be Hh regulated in the neural tube. In addition, we have uncovered at least 11 additional novel sites, some in known Hh targets and several in new putative target genes. The biological activities of these putative Gli enhancers were addressed using a combination of bioinformatics approaches, in vitro enhancer assays and, finally, direct analysis in transgenic mice. In addition to validating the basic methodology, the data provide interesting new information regarding the tissue specificity of a "generic" Hh response and insights into how morphogen signaling is interpreted at a transcriptional level. We are currently extending these studies to a direct examination of Gli targets in the embryonic mouse limb.

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Small molecule-directed protein mislocalization

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Rapid changes in the subcellular location of proteins are associated with many important biological events. We are developing a method for controlling protein's position using a membrane-permeable small molecule. The target protein is expressed as a fusion with a short tag that imparts high affinity for the small molecule. The drug then recruits an address signal, such as the one that directs nuclear export or import. We expect that this method will permit robust, reversible control over protein distribution. We are currently adapting this method for use in yeast, a model in which functional genomic studies should be possible.

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