IN BRIEF

GENE EXPRESSION

Embryonic stem cell-specific microRNAs.

Houbaviy, H. B. *et al. Dev. Cell* **5**, 351–358 (2003)

The authors identify a set of microRNAs in undifferentiated and differentiated mouse embryonic stem (ES) cells. Their sequences are similar and are encoded by loci that cluster within 2.2 kb of each other. Because their expression is repressed as the ES cells differentiate, the authors suggest that they might have a role in the maintenance of the pluripotent character of these cells and in the regulation of early mammalian development.

EVOLUTION

Molecular phylogenies link rates of evolution and speciation.

Webster, A. J. *et al. Science* **301**, 478

There are good theoretical reasons to think that the rates of genetic evolution and speciation should be linked, but empirical confirmation of a general relationship between the two has been lacking. In their careful analysis, Webster *et al.* show that these rates are correlated in 30–50% of 56 previously published DNA-based phylogenies. The authors suggest that a punctuated molecular clock, in which rapid genetic evolution is often linked to speciation, best explains this general pattern.

FUNCTIONAL GENOMICS

A large-scale, gene-driven mutagenesis approach for functional analysis of the mouse genome.

Hansen, J. *et al. Proc. Natl Acad. Sci. USA* August 2003 (10.1073/pnas.1633296100)

Gene traps — vectors that insert reporter genes at many sites throughout a genome — can be used to establish mouse embryonic stem (ES) cell libraries with mutations in most genes. Hansen *et al.* show that different gene traps have different insertional 'hot spots' in the mouse genome and so, when used in combination, complement each other. They also show that gene trapping can mutagenize all functional classes of genes and is as efficient as conventional gene targeting.

CANCER GENETICS

A mechanism of cyclin D1 action encoded in the patterns of gene expression in human cancer.

Lamb, J. *et al. Cell* **114**, 323–334 (2003)

Cyclin D1 (CD1) is overexpressed in many types of tumour, but exactly how it contributes to the development of cancer was previously unclear. Lamb *et al.* examined the microarray-expression profiles already available for a wide range of tumour types, for genes that are frequently co-expressed with CD1. Their sophisticated data-mining approach allowed them to identify a gene not previously associated with CD1 as a key effector of its influence on transcription. Their approach could be used to analyse many genes that are involved in cancer development.

DEVELOPMENT

Smoothening Hedgehog signalling

More than 25 years have passed since the original genetic screens in *Drosophila melanogaster* identified many of the genes involved in embryonic patterning. Although subsequent screens have placed many of these genes in specific signalling pathways, the precise mechanisms of how they control patterning have remained elusive. One such gene is *smoothened* (*smo*), which encodes a transmembrane protein that is essential for transmitting the Hedgehog (Hh) signal. On the basis of her new data, Joan Hooper now proposes a model for how this transmembrane protein induces distinct cellular responses to different Hh levels.

Hh signalling is imperative during the establishment of compartment boundaries, and acts as a morphogen to induce distinct cellular responses at different levels. All transcriptional responses to Hh are regulated by a balance between a repressor or activator form of the Cubitus interruptus (Ci) transcription factor. This balance is controlled by a regulatory complex of proteins that are in turn activated by Smo. In the absence of Hh, Smo is inhibited by another transmembrane protein, Patched.

Joan Hooper created chimeric and mutant forms of the Smo receptor to dissect how Smo interprets different levels of the Hh signal, and how this is translated into distinct signalling responses. Chimeric receptors were generated between Smo and the related Wingless (Wg) signal receptor Frizzled (Fz), and their activity was assessed in three ways: through alterations in Ci signalling, Hh target-gene activation and wing patterning. Not surprisingly, different chimaeras had different effects on either high or low levels of Hh signalling. A Smo–Fz chimaera that only contains the Smo cytoplasmic domain (FFS) can generate all the normal responses that are associated with the activation of Smo, but the receptor is activated by Wg and not Hh. Conversely, a chimaera that contains the Fz intracellular domain but is otherwise identical to normal Smo (SSF), interferes with cellular responses to high levels of Hh but not to low levels. Double-mutant analysis indicates that this chimaera titrates endogenous Smo receptor and acts in a dominant-negative manner to inhibit Hh signalling.

A truncated form of Smo that only contains the intracellular domain (SmoC) also affects the cellular response to high levels of Hh, much like SSF. But unlike SSF, SmoC also allows endogenous Smo to constitutively activate low-level responses. SmoC seems to act by titrating a member of the downstream regulatory complex, Costal.

Putting these genetic interactions into a model indicates that the Smo receptor can initiate all the responses that are associated with both high and low levels of Hh, but can also differentiate between these levels. Low levels of Hh could allow Smo to 'reveal' the cytoplasmic domain of the receptor, leading to low-level activation of Ci. At high levels of Hh, this effect would be amplified, causing Smo dimerization and allowing full activation of the downstream regulatory complex. This would generate increased levels of activated Ci. The responses of Smo to changes in Hh levels must now be tested at the molecular level, but it could be that all receptors related to Smo use a similar mechanism by which they translate different levels of an extracellular signal into distinct intracellular responses.

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Nature Publishing Group

References and links

ORIGINAL RESEARCH PAPER Hooper, J. E. Smoothened translates Hedgehog levels into distinct responses. *Development* **130**, 3951–3963 (2003)

ENCYCLOPEDIA OF LIFE SCIENCES Signal transduction pathways in development: Hedgehog proteins and their receptors