



DEVELOPMENTAL BIOLOGY

A converging pattern

Converting a morphogenetic field into a defined tissue or organ involves the precise interaction of a complex network of genes. The defining event in such a process is the discrete expression of so-called 'field-selector genes', which, in the case of the fruitfly wing, ensure that the cluster of cells in which they are expressed develop into a wing rather than into another organ. But how do selector genes orchestrate the development of complex structures and how do they impart specificity to globally deployed signalling pathways such as *Decapentaplegic* (Dpp) and *Notch*, which pattern the wing as well as many other organs? Investigating how selector genes direct the expression of field-specific responses has been the focus of a recent study by Guss *et al.* Their results show that the expression of wing-specific responses requires both wing-specific selector genes and commonly deployed signalling pathways.

The selector gene complex that specifies wing identity consists of two proteins, Vestigial (Vg) and Scalloped (Sd). The *sd* gene encodes a DNA-binding protein that is required cell-autonomously for the expression of wing-patterning genes such as *cut*, *spalt* and *vg*. Sd binds directly to the *cis*-regions of the target genes it regulates. In addition, mutating the Sd-binding sites in the promoters of *cut*, *spalt* and *vg* eliminates their expression. It is therefore possible that, in the wing, field-selector genes control directly the expression of all target genes, rather than controlling only a few members of the gene-regulatory network. However, *cut*, *spalt* and *vg* are also known targets of the Notch and Dpp signalling pathways. This observation led Guss *et al.* to test whether field-specific genes and commonly deployed signalling pathways pattern the wing field by converging on the control regions of the same genes. Indeed, only when binding sites for both selector and signalling genes are present on a synthetic promoter construct can wing-specific gene expression and patterning occur.

This study has made a step towards clarifying the relationship between two genetic systems that are required to specify and pattern a structure, by showing that both systems depend on each other. Although these results are specific to wing development, an obligatory combinatorial input on target promoters might be a general mechanism by which selector genes work with signalling pathways to control the extensive genetic network that specifies the development of complex structures.

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References and links

ORIGINAL RESEARCH PAPER Guss, K. A. *et al.* Control of a genetic regulatory network by a selector gene. *Science* 12 April 2001 (10.1126/science.1058312)

FURTHER READING Mann, R. S. & Morata, G. The developmental and molecular biology of genes that subdivide the body of *Drosophila*. *Annu. Rev. Cell Dev. Biol.* 16, 243–271 (2000)

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MOUSE MODELS

A hit-and-run on sporadic cancer

Mouse models for tumorigenesis have traditionally mimicked hereditary rather than sporadic cancers, as it is relatively straightforward to breed mice with a germline mutation that predisposes them to cancer. However, the development of a modified 'hit-and-run' gene-targeting technique, described by Jacks and colleagues in *Nature*, is set to change this.

The technique targets the *K-ras* oncogene — which is mutated in 30% of human tumours — and the advance comes not in the 'hit' step, in which the mutated allele is inserted into the genome of embryonic stem cells, but in the 'run' step. The authors capitalized on the fact that mitotic recombination occurs 10^{-3} – 10^{-7} times per cell division. By building a construct that could recombine to produce an oncogenic *ras* gene, they can trigger tumorigenesis spontaneously *in vivo* — as would occur in sporadic cancer.

The authors generated two constructs, *K-ras^{LA1}* and *K-ras^{LA2}*. Each carried two copies of exon 1, in which codon 12 of one or both of the copies, respectively, was mutated from glycine to aspartic acid, leading to a constitutively active K-ras protein. Recombination *in cis* resulted in oncogenic *K-ras* in 50% of recombination events in *K-ras^{LA1}* mice, but in 100% of events in *K-ras^{LA2}* mice. *K-ras^{LA}* mice had reduced lifespans — *K-ras^{LA2}* mice the shortest — compared with wild-type mice, and developed many tumours. Both strains had a similar

tumour spectrum, and all mutants developed tumours that histopathologically resembled human non-small-cell lung cancer. Approximately 30% of the mice also developed thymic lymphoma and skin papilloma. Biochemical analyses showed that tumour cells carried the recombined, oncogenic *ras* allele.

Surprisingly, the mice did not develop carcinomas of the colon or pancreas, cancers frequently associated with the *K-ras* oncogene in humans. As carcinomas with *K-ras* mutations also often have defects in the p53 pathway, the authors crossed *K-ras^{LA1}* mice with *Trp53*-deleted mice. *Trp53^{+/-}* and *Trp53^{-/-}* mice, when carrying the *K-ras^{LA1}* allele, showed a further reduction in survival compared with parental strains. Although these mice had a broader range of tumours — 30% developed haemangiosarcomas and fibrosarcomas — colonic and pancreatic tumours still did not occur. Goals for the future will therefore be to understand why this oncogene so consistently results in lung cancer in mice and to refine the technique to create models of the tumour types that occur in humans with *K-ras* mutations.

With new initiatives to develop better mouse models of cancer, this is an exciting time for the cancer research community. This study by Johnson *et al.* is an early fruit of such an initiative, and no doubt more will follow in the future.

Emma Greenwood, Associate Editor,
Nature Reviews Cancer

References and links

ORIGINAL RESEARCH PAPER Johnson, L. *et al.* Somatic activation of the *K-ras* oncogene causes early onset lung cancer in mice. *Nature* 410, 1111–1116 (2001)

WEB SITE Mouse Models of Human Cancer Consortium

