DEVELOPMENTAL BIOLOGY

All about my mother

Mothers, it would seem, were designed to meddle in our affairs right from the word go, as maternal gene products direct many embryonic processes before zygotic transcription gets going. To find out just what these genes might be, Mary Mullins' laboratory has carried out the first genetic screen of its kind in zebrafish, and has identified 68 mutants that should help to define the maternal and paternal contribution to vertebrate embryonic development.

Conventional zygotic screens are useless for picking up mutations that affect the very early stages of development, as zygotic gene expression has not yet begun. Mullins and colleagues therefore carried out a maternal-effect screen, involving a four-generation crossing scheme that was designed to maximize the recovery and propagation of mutant lines. Embryos of mothers that were homozygous for a given mutation were scored for abnormalities 24 h after fertilization. In this way, 68 maternal-effect mutations were found, which were divided into 2 groups — described in separate publications — according to whether they affect embryos before or after the mid-blastula transition, which marks the start of zygotic transcription.

The first paper describes the phenotype of 15 such mutants, which the authors classify into 5 groups, including those that affect egg activation and animal–vegetal polarity. The second paper focuses on 13 of the 48 mutations that affect the embryo after zygotic gene activation; these 'late' mutants also fall into 5 phenotypic classes, including those that affect cell viability and the body plan. Although the focus was on maternal genes, the screen also surprisingly picked up five paternal-effect mutants, which defied expectations by having substantial developmental effects.

Systematic, large screens such as this usually mark the beginning of many years of work into understanding which genes and pathways might be at work in the early vertebrate embryo, just as the output of maternal-effect *Drosophila melanogaster* screens has occupied hundreds of fly geneticists for years. In this case, the method is just as noteworthy as the results, as some inspired planning has allowed the authors to genetically map some of the mutations with relative ease.

Tanita Casci

References and links

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WEB SITE

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CANCER GENETICS

A guardian and a suppressor

There are some fundamental processes in biology that we would expect to be conserved across all phyla. And yet some of them use a surprising variety of molecular mechanisms. A recent report by McPherson *et al.* shows that the MUS81 endonuclease, which is involved in processing branched DNA structures in yeast, such as those found in stalled replication forks, is required in mammals for genomic stability and tumour suppression.

To clarify the role of *Mus81 in vivo*, the authors knocked out the gene in mice. Based on the role of Mus81 in yeast, they expected the mice to show meiotic recombination defects, such as infertility. To their surprise, the animals were fertile with no defects in gametogenesis. Normal gene targeting in the *Mus81*$^{-/-}$ embryonic stem (ES)-cell and B- and T-cell lineage (the ontogeny of which requires DNA rearrangements) confirmed that *Mus81* is not required for a cell to cope with dsDNA breaks.

But *Mus81* knockout mice do have a phenotype — mutant ES cells are hypersensitive to the alkylating agent mitomycin C, indicating that the gene might be involved in repairing mitomycin-C-induced DNA interstrand crosslinks. *Mus81* also seems to act as a haploinsufficient genome caretaker — loss of even one copy of *Mus81* leads to aneuploidy and other chromosomal defects.

Although at first glance, mutant mice seem to be normal, the authors found that only 27% of homozygotes and 50% of heterozygotes were healthy and survived through their first year. Many had tumours, mainly non-Hodgkin's lymphomas, which at the cellular level were associated with aneuploidy. Because *Mus81* homozygotes and heterozygotes were equally susceptible to cancer, both copies of *Mus81* must be required for its tumour-suppressor function — just as two copies are required for genome integrity.

Although MUS81 is not alone in being a haploinsufficient tumour suppressor, it is at odds with the common view that tumorigenesis requires the loss of both copies of a tumour suppressor. Mechanistically speaking, the genomic instability caused by *Mus81* haploinsufficiency might facilitate tumorigenesis, for example, in pre-neoplastic lymphocytes. However, it remains to be seen whether the model that the authors propose is correct — that is, that a 50% reduction in the amount of MUS81 protein in heterozygotes is not sufficient to resolve intermediate DNA structures that form during DNA repair.

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References and links

ORIGINAL RESEARCH PAPER McPherson, J. P. *et al.* Involvement of mammalian Mus81 in genome integrity and tumour suppression. *Science* **304**, 1822–1826 (2004)