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HUMAN GENETICS

Good housekeeping

How do mutations in ubiquitously expressed housekeeping genes cause tissue-specific defects? This question often comes up in cancer genetics because there are several examples of mutations in genes that have general functions and yet cause cancer in a highly restricted range of tissues. A new and striking example of this has been found by a European consortium that has identified a tumour suppressor gene that predisposes to leiomyomata (smooth muscle tumours). The gene encodes fumarate hydratase (FH), one of the enzymes in the citric acid cycle.

The consortium have been pursuing the gene for a dominant familial form of leiomyomatosis that they had previously mapped to chromosome 1. As reported in *Nature Genetics*, they narrowed down the critical region in a large group of affected families to a 1.6-Mb interval, which contained 6 known and more than 50 predicted genes. The authors found that mutations in only one of these genes — *FH* — were associated with tumour susceptibility. Among them were nonsense and frameshift mutations, and enzymatic assays confirmed that they cause a significant reduction in FH activity. The *FH* gene also behaves as a typical tumour suppressor gene — the majority of tumours studied had lost the wild-type *FH* allele. The results led to the clear conclusion that loss of FH activity can cause leiomyomata in these families.

Interestingly, mutations in *FH* are also associated with a second condition, simply referred to as FH deficiency.

This recessive condition is very severe, and usually results in the death of affected infants within a few months of birth. Comparing the nature and positions of *FH* mutations in patients with FH deficiency against those with leiomyomatosis, led the authors to conclude that FH deficiency is probably the result of only a partial reduction in FH activity. By contrast, the mutations in the leiomyomatosis patients tend to be more severe (although the patients are heterozygous), and when the wild-type allele is lost in the tumour, little activity is detectable.

But the question remains: how do loss-of-function mutations in the housekeeping gene *FH* cause tumours specifically in smooth muscle? The authors discuss the possibility that a defect in the citric acid cycle might lead to alterations in oxidative metabolism, and in turn to deregulation of the cell cycle in smooth muscle cells.

As an understanding of this association dawns, the consequences of FH dysfunction might become a valuable example of how genotype and cellular physiology intersect to give rise to a tissue-specific phenotype.

Mark Patterson

References and links

ORIGINAL RESEARCH PAPER The Multiple Leiomyoma Consortium. Germline mutations in *FH* predispose to dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cell cancer. *Nature Genet.* 2002 (DOI 10.1038/ng849)

WEB SITES

Encyclopedia of Life Sciences:

<http://www.els.net>

Citric acid cycle

Ian Tomlinson's lab:

<http://science.cancerresearchuk.org/research/loc/london/lifch/tomlinson/?version=1>

Richard Houlston's lab:

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