CANCER GENETICS

Visceral feedback

Most sporadic and inherited colon cancers result from the constitutive activation of Wnt signalling caused by loss of the tumour suppressor protein APC or by mutations in β-catenin. In response to the Wnt signal, β-catenin is translocated to the nucleus where, together with LEF1 (lymphoid enhancer factor) and TCF (T-cell factor), it activates the transcription of target genes. A recent paper now identifies *LEF1* itself as a target of Wnt signalling in colon cancer cells, indicating that an aberrant positive-feedback loop is involved in gene activation in colon cancer.

Hovanes and colleagues turned their attention to *LEF1* because they noticed its abnormal expression in colon cancer cells. *LEF1* normally produces two transcripts, but in colon cancer cells, only the longer (3.6-kb) transcript is present. The 3.6-kb *LEF1* transcript encodes a DNA-binding domain and a β-catenin-binding domain, whereas the short (2.2-kb) form encodes only the DNA-binding domain. The authors show that the short message is transcribed from an internal promoter and acts as a natural dominant negative — although it binds to its DNA targets it cannot activate them because it doesn't interact with β-catenin.

Using reporter constructs, the authors show that β-catenin–TCF complexes strongly activate *LEF1* transcription, but mainly from its upstream promoter. Because only the 3.6-kb form is present in colon cancer cells, the authors suggest that, in these cells, the promoter for the shorter message is downregulated or switched off, whereas the other promoter is activated. In the absence of the natural dominant-negative form, full-length LEF1 is free to interact with β-catenin and so to activate target genes, which leads to even higher levels of LEF1.

Together with β-catenin, the high levels of LEF1 will activate downstream target genes, and it will be important to identify the key targets involved in carcinogenesis in the colon. It would also be useful to know why dysregulated Wnt signalling activates transcription of only the long *LEF1* message. Nevertheless, the work of Hovanes *et al.* reveals an important new mechanism involved in colon cancer — a positive-feedback loop of Wnt signalling, with *LEF1* at its centre.

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WEB SITE Marian Waterman's lab

PLANT GENETICS

Turning off transposons

Transposons, Barbara McClintock's 'jumping genes', are the ultimate parasite. Intimately entwined with their host's DNA, they passively replicate along with it. Less benignly, they can spread in a genome, disrupting and mutating genes as they go. Two recent studies on *Arabidopsis* demonstrate that epigenetic modification can prevent this destructive jumping by showing that demethylating otherwise dormant transposons activates and mobilizes them. It had previously been known, both in *Arabidopsis* and mice, that transposons become transcriptionally active in methylation-deficient backgrounds. These new studies go further by showing that demethylation also mobilizes transposons.

Transposon-induced colour variegation in maize

Both studies looked at the activities of transposons in *ddm1* (decrease in DNA methylation) *Arabidopsis* mutants. *DDM1* encodes a protein that is similar to the chromatin-remodelling factor SWI2/SNF2 and is essential for silencing many methylated and repeated genes in *Arabidopsis* — *ddm1* mutants have hypomethylated genomes.

Taking a bioinformatics approach, Martienssen and colleagues searched the recently completed *Arabidopsis* genome sequence and identified 22 transposons related to the *Mutator* transposable elements from maize. In wild-type Columbia ecotype plants, these transposons are methylated and dormant, but in *ddm1* plants they are hypomethylated and transcribed. In addition, more than one in eight *ddm1* plants had extra *Mutator*-like transposons, indicating that complete transposition had occurred.

Conversely, Kakutani and colleagues began by investigating the developmental abnormalities of *ddm1* plants. One dwarfing *ddm1* mutant phenotype was found to be caused by a DNA insertion that disrupted a gene on chromosome 3, which is involved in synthesis of the plant hormone brassinosteroid. The insertion, when sequenced, seemed to have been caused by the transposition of an 8,479-bp region from chromosome 2. This region, named *CAC1*, resembled a CACTA family transposon, the members of which have previously been identified in both maize and *Antirrhinum*. Searching the *Arabidopsis* genome turned up only four sequences related to *CAC1*, but in 11 out of 12 *ddm1* lines investigated there were many more copies scattered throughout all 5 chromosomes, presumably produced by transposition of 'wild-type' *CAC* transposons.

The precise mechanisms involved are yet to be established, but these results show that epigenetic control of gene expression has been co-opted to guard against the chaos caused by unfettered transposon activity. Or, given that maintenance of a stable genome is essential for any organism, perhaps this defence function came first.

Christopher Surridge,
Senior Editor, Nature

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WEB SITES Rob Martienssen's lab | Tetsuji Kakutani's lab