Future research will undoubtedly investigate how specific methylation events are controlled in normal cells and during tumour development. Understanding these mechanisms will have important therapeutic implications: changes in DNA methylation are more readily reversible than mutations or deletions, so a deeper knowledge of how DNA methylation goes awry in cancer might pave the way to restoring the function of tumour-suppressor genes in human cancer.

Barbara Marte,
Editor, Nature Cell Biology

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WEB SITE

Bert Vogelstein's lab: <http://www.hhmi.org/research/investigators/vogelstein.html>

CMT3 has a chromodomain made the authors wonder whether CMT3 could bind directly to Lys9 of histone H3, as does HP1, which binds to methylated, heterochromatic regions. Their *in vitro* studies and binding assays of tagged CMT3 and histone H3 in *Escherichia coli* gave negative results — instead, CMT3 turned out to bind directly to the *Arabidopsis* HP1.

On the basis of their findings, the authors propose the following model. HP1 is attracted to Lys9 of histone H3, once it has been methylated by KYP. HP1 then binds to CMT3, thus bringing it to the site of histone methylation. It is then up to CMT3 to methylate the DNA. Although this model awaits an *in vivo* validation, it suggests the existence of a eukaryote-wide mechanism for attracting DNA methyltransferases to chromatin, in which HP1 has a central role.

Magdalena Skipper

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SIGNAL TRANSDUCTION

Legless flies for wingless research

Funny-looking fruitflies have provided the starting point for many interesting lines of research. For example, the *Drosophila wingless* mutant led to the discovery of the Wingless (or Wnt in vertebrates) signalling pathway, which is highly conserved and is involved in many aspects of development. And now a fly with no legs has helped to unearth two new components in the Wingless pathway. The broader significance of these findings is emphasized by the identification of human counterparts for both components, one of which has been implicated in cancer.

When a cell is exposed to the Wingless signal, reduced protein degradation causes the level of the protein Armadillo (β -catenin) to rise in the cytoplasm. Armadillo then translocates to the nucleus where, in combination with the transcription factor Pangolin (TCF), it activates the transcription of key genes. Little is known about this part of the pathway, prompting Kramps *et al.* to look for new genes that might be involved in transcriptional activation.

They started with a genetic screen for mutants that could suppress an overactive Wingless signalling pathway. As well as finding mutations in genes that encode known components of the pathway, they also found a new locus on chromosome 4. Although welcome, this also created a problem — chromosome 4 doesn't recombine during meiosis, ruling out conventional approaches for genetic mapping. The authors therefore devised a method for generating chromosomal deletions, which they used in a complementation analysis. They defined a critical region of 150 kb, and then sequenced all open reading frames in this interval in the suppressor mutants. One chromosome 4 gene was mutated in several mutants, and they named it *legless*, after the phenotype of certain *legless* compound heterozygotes.

Legless protein is located in the nucleus, and epistasis analysis showed that it acts downstream of Armadillo in the Wingless pathway. The authors also identified a second new gene — in a two-hybrid screen — that encodes a protein that binds to Legless. They called this gene *pygopus* — after a genus of lizards with no legs — because of similarities between the *pygopus* and *legless* phenotypes. Further genetic and biochemical experiments led the authors to propose a model for the way these new genes work. The main — and perhaps only — function of Legless is to link

Pygopus to Armadillo in the nucleus. Pygopus then participates in the transcriptional activation of Wingless target genes.

There are human genes related to both *legless* and *pygopus*, which can each complement mutations in the fly. Moreover, the functional homologue of *legless* is *BCL9*, a gene that has previously been implicated in the development of certain B-cell tumours. The link between Wingless/Wnt signalling and colon cancer is already well established, but these new results suggest that defects in this signal-transduction pathway might underlie other forms of cancer as well, and highlight some interesting new avenues for anticancer therapy. Although there are many details still to figure out, the identification of Legless and Pygopus as two new factors that are specifically required for Wingless/Wnt signalling in the nucleus is a significant step forward.

Mark Patterson

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WEB SITES

Konrad Basler's lab: <http://www.unizh.ch/imb/basler/>
The Wnt gene homepage: <http://www.stanford.edu/~musse/wntwindow.html>