EPIGENETICS

Early signs of trouble ahead

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UniProt:
EZH2[http://www.expasy.org/
uniprot/Q15910](http://www.expasy.org/uniprot/Q15910)

Epigenetic marks that are laid down early in normal development predispose certain genes to cancer-promoting DNA-methylation events. This is the conclusion of two recent studies that provide a new connection between cancer development and stem-cell properties.

Silencing of tumour suppressor genes by abnormal DNA methylation is a key feature of cancer cells. Schlesinger and colleagues were interested by the fact that, during normal development, promoter methylation is accompanied by certain histone modifications that are typical of heterochromatin. They found a similar correlation in colon cancer cells between one such heterochromatic mark — trimethylation of histone H3 at lysine 27 (H3K27) — and promoter hypermethylation. Importantly, they also showed that the methylated target genes are

pre-marked with H3K27 before tumorigenesis, as shown by the fact that the same genes had this mark in embryonic stem (ES) cells and a range of other undifferentiated cell types.

How is this pre-marking established? H3K27 trimethylation is carried out by **EZH2**, a component of the Polycomb group complex PRC2. Several groups have recently shown that this complex is required in ES cells to keep differentiation-promoting genes in a repressed but activatable state. Schlesinger and colleagues wanted to know whether PRC2 binding predisposes these genes to hypermethylation in cancer. The same question was investigated by a second group, Widschwendter and colleagues. Using genome-wide binding information for PRC2 components that had been previously published for ES cells, both groups showed that genes that are marked by PRC2 components in these pluripotent cells are significantly more likely to undergo later hypermethylation in colon cancer cells. The same was found to be true for a range of other tumour types.

The two groups concluded that this pre-marking is likely to take place early in development. Schlesinger and colleagues supported this theory using a bioinformatic analysis that showed that the hypermethylated genes from their colon cancer cell line are not only marked by PRC2 components in several other cell types, but actually carry potential PRC2 binding elements within the DNA itself. This indicates pre-

marking in an early precursor cell, although not necessarily in ES cells.

Both groups suggest that the pre-marking of certain genes leads to hypermethylation due to crosstalk between PRC2 components and DNA methyltransferases (DNMTs). In this way, the normal repression of these genes in precursor cells can be aberrantly converted to a permanently silenced state, which prevents full differentiation and predisposes cells to become cancerous. Widschwendter and colleagues point out that PRC2 targets in breast and colorectal cancer cells include genes other than those that are pre-marked in stem cells, and these additional targets are not prone to cancer-specific hypermethylation. Therefore, DNMTs are likely to be recruited by PRC2 pre-marking in an early event *en route* to oncogenesis, when cancer cells still show a stem-cell-like epigenetic signature.

The question now is: what triggers this abnormal DNA methylation? The regulation of DNMTs early in the development of cancer should prove to be an important area of investigation.

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ORIGINAL RESEARCH PAPERS

Widschwendter, M. *et al.* Epigenetic stem cell signature in cancer. *Nature Genet.* 31 December 2006 (doi:10.1038/ng1941) | Schlesinger, Y. *et al.* Polycomb-mediated methylation on Lys27 of histone H3 pre-marks genes for *de novo* methylation in cancer. *Nature Genet.* 31 December 2006 (doi:10.1038/ng1950)

FURTHER READING Feinberg, A. P. *et al.* The epigenetic progenitor origin of human cancer. *Nature Rev. Genet.* 7, 21–33 (2006) | Sparmann, A. & van Lohuizen, M. Polycomb silencers control cell fate, development and cancer. *Nature Rev. Cancer* 6, 846–856 (2006)