Epigenetics

Surveillance team against cancer

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Variations in the control of a phenomenon known as parental imprinting influence the likelihood of tumour development. These new findings may tie in with an earlier concept of 'two-phase' carcinogenesis.

Cancer is often viewed as a genetic disease — one that results when the DNA sequence of key genes is mutated, leading to the removal of protective roadblocks and/or to the unchecked proliferation of cells. In recent years, however, it has become clear that 'epigenetic' malfunctions can also contribute to cancer development. These malfunctions can be defined as being due to relatively stable changes in gene expression without changes in the DNA sequence of the gene. They are often detected by the chemical addition or removal of methyl or acetyl groups that cause, or signal, a change in the structure of chromatin, the DNA–protein complex that forms chromosomes. When their normal modifying effects on gene expression are deregulated, tumours can arise.

Do some of the many 'surveillance' mechanisms that protect us from cancer act at the epigenetic level? One way to approach this problem is to ask whether mechanisms that influence the stringency of maintaining epigenetic modification can modulate the risk of cancer development. In a paper just out in *Science*[1], and in a previous study[2], Andrew Feinberg and colleagues address this issue.

The idea that changes in the epigenetic regulation of gene expression may contribute to the initiation or progression of tumour development was initially viewed with scepticism. But this view has changed radically, particularly in the past decade. Three kinds of frequent epigenetic changes have been identified in tumours. The first is genome-wide hypomethylation, which leads to the activation of many genes that are normally silenced in adult tissues. Second, tumour-suppressor genes can be inactivated by dense hypermethylation of their upstream regulatory sequences, with consequences that are similar to those resulting from inactivation of the same genes through mutation or deletion. Finally, loss of parental imprinting can occur. This is a specific form of epigenetic modification that involves inactivating either the maternally derived or the paternally derived copy of a particular gene in the offspring.

Given these findings, it would seem reasonable to suppose that organisms must have ways of keeping tabs on the epigenetic status of DNA, in the same way that other aspects of tumour development can be checked. At least three kinds of tumour surveillance have been firmly established[3], and their importance is demonstrated by what happens when they break down. The word 'surveillance' was first brought into the cancer field through the 'immune surveillance' hypothesis, which suggested that immune defence mechanisms nip precancerous cells in the bud. Later, however, it turned out that the immune system protects us mainly, if not exclusively, from the growth of potentially neoplastic cells that are initiated by viruses. The main examples include tumours associated with the human papillomaviruses, non-Hodgkin's lymphomas driven by Epstein–Barr virus, and Kaposi's sarcoma associated with human herpesvirus 8.

A second, phylogenetically more ancient and more powerful surveillance function is provided by the repair of damaged DNA sequences. The loss or impairment of DNA-repair enzymes is associated with multicancer syndromes. Finally, there is powerful intracellular surveillance, which detects the illegitimate activation of oncogenes (proliferation-driving genes) and can trigger programmed cell death. The crippling of major cell-death pathways is a universal feature of cancer.

So, is there also epigenetic surveillance? Feinberg and colleagues' findings[1,2] — which indicate that variations in the stringency of parental imprinting may influence the likelihood of tumour development — suggest that there is. In their earlier paper[2], they found that loss of imprinting of the insulin-like growth factor II (*IGF2*) gene — a feature of many human cancers — can be detected in the peripheral blood lymphocyte cells of about 10% of the normal human population. This suggests that the stringency of the postnatal maintenance of *IGF2* imprinting is genetically determined; the authors also found that this 10% of the population has a 3.5–5-fold increase in the risk of developing colorectal adenomas; thus, instability of the mechanism for maintaining imprinting is related to the risk of neoplastic disease.

In their latest paper[1], the authors provide experimental evidence that supports their interpretation of the human data, and suggest a possible mechanism. In this study, hybrid mice were generated by crossing two genetically engineered mouse strains. The females used for the cross were heterozygous for a deleted differentially methylated region, or DMR (heterozygosity here means that one of the two copies of the relevant chromosome contained this region, whereas the other did not). Inheritance of this deletion from the mother leads to expression of *IGF2* from both maternally and paternally derived gene copies — thus corresponding to loss of imprinting. The males entering the hybrid cross came from the Min strain, which carries a mutation in the adenomatous polyposis coli (*APC*) gene. Mutations in *APC* provide a strong predisposition to familial colonic polyposis, a precancerous condition in humans and mice.

The result of this cross was that all offspring carried the *APC* mutation, but only half of them inherited the imprinting defect. Strikingly, the frequency of intestinal adenomas was twice as high in the mice with the imprinting defect compared with their littermate controls. Also, their intestinal crypts were longer and showed increased staining for proteins that are characteristic of intestinal-cell progenitors. This indicated that the differentiation of these cells to more specialized intestinal cell types was delayed.

These observations[1] show, for the first time, that the impairment of normal parental imprinting may interfere with cellular differentiation and thereby increase the probability of cancerous development. Taken together with the data in the earlier paper[2] — which showed person-to-person differences in the epigenetic silencing of *IGF2* that are related to a predisposition to colon cancer — the findings indicate that cancer susceptibility may be influenced by differences in the stringency of epigenetic control. This is consistent with earlier work showing that inbred mouse strains may differ in the activity of enzymes involved in DNA methylation[4].

In more general terms, the findings[1,2] also show that mutation of a 'cancer gene' (*APC*) and an epigenetically imposed delay in cell differentiation may drive tumour development synergistically. This inference is reminiscent of the early concept of two-phase carcinogenesis — by 'initiation' and 'promotion' — advanced by Isaac Berenblum[5]. In general, initiation may correspond to mutation or epigenetic silencing, whereas promotion probably occurs through epigenetic modification. More specifically, Berenblum showed that impairment of differentiation is an essential part of tumour promotion.

Feinberg and colleagues' results are consistent with this idea, but they also raise new questions. In particular, it will be necessary to explore the ways in which the loss of imprinting of a tumour-unrelated gene may contribute to the delay in differentiation of a specialized tissue, and influence its predisposition to cancer. ■

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