gene mutations expose themselves by their recurrence in multiple tumours. However, there are certain tumour types in which very few recurrently mutated genes — often only one or even none per tumour — have been detected, namely in childhood tumours such as medulloblastoma[7], neuroblastoma[8] and rhabdoid tumours[9]. All current sequencing technologies sometimes miss mutations[6], but the fact that this paucity of mutations was observed with diverse technologies, and only in childhood tumours, makes it unlikely that it results from technical artefacts. Now, these two papers report that posterior fossa ependymomas also seemingly lack recurrently mutated genes.

If not gene mutations, what else could cause cancer? It has long been suspected that defective epigenetic modifications — that is, non-sequence-changing alterations, such as the methylation or acetylation of DNA or DNA-associated chromatin proteins — might also be oncogenic. Several genes encoding enzymes that apply or remove these modifications have been shown to be mutated in tumours, confirming a role for epigenetics in cancer[10], but such mutations were not detected in the ependymoma studies. However, Mack *et al.* did find increased DNA methylation of specific genes, as well as silencing of their expression, in type A, but not type B, posterior fossa ependymomas.

Expression of these same genes was previously found to be silenced in embryonic stem cells by the protein complex PRC2 (ref. 11), which mediates a common epigenetic modification: trimethylation of the amino acid lysine at position 27 in the histone protein H3 (H3K27me3). Indeed, Mack and colleagues found H3K27me3 marks on many of the genes with DNA methylation in posterior fossa type A tumours. They therefore hypothesize that the repression of these genes by PRC2 keeps these tumour cells in an embryonic and proliferative state.

A lack of model systems for experimental studies of posterior fossa ependymoma did not allow crucial testing of this hypothesis, and these data remain correlative, but preliminary testing of drugs targeting DNA methylation and H3K27me3 inhibited the proliferation of type A tumour cells *in vitro*. The key question emerging from these findings is whether and how a cell can escape the normal regulatory mechanisms governing epigenetic modifications such that oncogenic gene-expression patterns can persist, without having DNA-sequence mutations.

What remains are posterior fossa type B ependymomas, for which neither tumour-driving gene mutations nor epigenetic changes have yet been found. Both groups of authors refrain from any interpretation of this. Type B tumour cells differ from type A tumour cells by typically containing gains and losses of entire chromosomes or large chromosomal fragments[5]. Chromosomal deletions occur frequently in almost all tumour types and are usually interpreted as part of a two-hit inactivation of a tumour-suppressor gene, in which one copy of the gene is destroyed by a mutation and the other copy by a deletion. However, genome-sequencing data have shattered the expectation that deletions will always involve a tumour-suppressor gene. Neuroblastoma tumours, for example, frequently show deletions of regions of chromosomes 1 and 11, but no recurrently mutated tumour-suppressor genes have been found on the corresponding section of the paired chromosome[8,12,13].

Thus, it may be that some such deletions have an entirely different role in cancer. The deleted areas usually encompass hundreds of genes, and changes in the expression of large numbers of genes can be highly pathogenic. For example, one extra copy of chromosome 21 causes Down's syndrome, and third copies of any other chromosome are mostly lethal. Speculatively, cancer initiation could occur when a deleted region encompasses several inhibitory genes of a particular cell-signalling pathway, and a gained region contains several positive regulators of that pathway. The resulting modest changes in expression of each individual gene could together exponentially activate the pathway, and may drive cancer.

It will be challenging to test whether chromosomal gains and losses, or epigenetic modifications without gene mutations, can indeed drive cancer development. The clinical implications of such alternative oncogenic routes would, however, be far reaching. Much research focuses on drugs that target gene mutations. The C11orf95–RELA fusion protein identified by Parker and colleagues provides a new target for drugs against supratentorial ependymoma, but the treatment of posterior fossa tumours might require a fundamentally different approach. ■

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50 Years Ago

In a statement made simultaneously in both Houses of Parliament on February 6, the Government announced that as a result of investigations undertaken jointly both the British and the French Governments considered that the construction of a rail Channel tunnel was technically possible, and that in economic terms it would represent a sound investment of their resources. The two Governments had therefore decided to go ahead with this project, and the next step would be to discuss further in particular the legal and financial problems involved.
From *Nature* 29 February 1964

100 Years Ago

The exceptionally mild character of the present winter is being maintained until its close, and for a persistent continuance of warm days in January and February it surpasses all previous records. At Greenwich the thermometer in the screen was above 50° for eighteen consecutive days from January 29 to February 15. Previous records since 1841 have no longer period than eleven days, in the months of January and February combined, with the thermometer continuously above 50°, and there are only four such periods … The persistent continuance of the absence of frost is also very nearly a record … The maximum temperatures in the two months have seldom been surpassed. In many respects there is a resemblance between the weather this winter and that in 1899, when in February blizzards and snowstorms were severe on the other side of the Atlantic, with tremendous windstorms in the open ocean, whilst on this side of the Atlantic the weather was exceptionally mild. It is to be hoped that this year we shall be spared the somewhat sharp frosts experienced in the spring of 1899.
From *Nature* 26 February 1914