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The path to retinoblastoma

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Abstract

Genomic analyses of tumours of the childhood cancer retinoblastoma reveal a low mutation rate, challenging the view that genomic instability is crucial for its progression. The work also identifies a new therapeutic target.

Retinoblastoma is a rare tumour that affects retinal cells in the eyes of children. Analyses of familial and sporadic cases of this cancer, backed by studies in genetically engineered mice, have shown that loss of function of the tumour-suppressor protein RB1 (also known as RB) is required for the development of most, if not all, tumours of this type. However, it is not clear how RB1-deficient retinal cells progress to malignant tumour cells¹. In addition, emerging evidence that loss of RB1 function can induce genomic instability² has raised the tantalizing possibility that RB1-deficient retinal cells might be predisposed to accumulating many additional mutations, further complicating the identification of mutations that contribute to the development and maintenance of retinoblastoma. On page 329 of this issue, however, Zhang *et al.*³ demonstrate that retinoblastoma genomes have very few recurrent mutations in genes other than *RB1*. Instead, the expression of cancer-related genes is affected by epigenetic modifications on chromosomes, which do not affect DNA sequence but are inherited after cell division.

To identify mutations that could cooperate with loss of RB1 function in tumour development, Zhang and colleagues³ sequenced and compared the genomes of normal tissue and retinoblastoma tumours from four patients. The researchers found that *RB1* was the only known cancer-related gene consistently mutated, and that the retinoblastomas had 15-fold fewer total mutations than other types of solid tumour whose genomes have been sequenced⁴.

Next, the authors searched for epigenetic alterations and for abnormal gene expression in retinoblastoma cells. They identified the gene that encodes the protein kinase enzyme SYK as a potential oncogene whose expression is consistently higher in retinoblastoma cells than in normal immature retinal cells. Moreover, the activity of SYK was essential for the growth of retinoblastoma cells. The authors also show that certain small molecules that selectively inhibit SYK activity induce the death of retinoblastoma cells in a mouse model of the disease.

These findings³ indicate that SYK may be a promising target for treating patients with retinoblastoma. *SYK* was not identified in previous searches for genes with a role in this cancer because it is not mutated or structurally rearranged in retinoblastoma. Therefore, Zhang and colleagues' study emphasizes the importance of high-throughput approaches that integrate genome sequencing with gene-expression analysis and epigenomics to identify cancer genes.

Low mutation frequency has also been observed⁵ in medulloblastoma (a type of brain tumour that affects children), suggesting that it could be a general feature of childhood cancers. A possible explanation for this difference between the cancers of children and adults is that childhood tumours arise in cells that are naturally undergoing rapid developmental growth, with fewer brakes on their proliferation than cells in adults. An alternative explanation is that, in children, these cells are negotiating crucial developmental checkpoints that are susceptible to corruption, leading to incomplete or abnormal maturation. In both cases, only a few mutations would be needed to trigger the cellular changes associated with cancer.

Furthermore, epigenetic changes in children and excessive mutations in adults may have similar roles in cancer development. Another childhood cancer, Wilms' tumour, also has a relatively stable genome and displays an increased variation in DNA-methylation patterns compared with normal cells⁶. RB1-deficient retinal cells may be particularly susceptible to this tumour-formation mechanism, because RB1 interacts with the machinery that controls the epigenetic status of cells, including enzymes that remodel chromatin (DNA–protein complexes) and other enzymes that add methyl groups to DNA¹. Thus, childhood cancers such as retinoblastoma may carry epigenetic abnormalities that change gene expression and are stably propagated through subsequent cell divisions, helping to maintain tumour-associated features.

If this model is correct, it is possible that RB1-deficient tumours in adults — such as small-cell lung cancer and some breast, prostate or blood cancers — also display epigenetic changes that are crucial for tumour development and maintenance. Future experiments, including integrated genomic analyses, may provide the answer.

The underlying mechanism of alterations in gene expression by epigenetic means in retinoblastoma is still unclear. But Zhang and co-workers' observation³ that 13% of these tumours show recurrent mutations in the *BCOR* gene offers a possible explanation. The BCOR protein is highly expressed in the fetal retina and is essential for eye development, as evidenced by a congenital eye disorder, syndromic microphthalmia, which results from a heritable mutation in *BCOR*⁷. BCOR associates with proteins that repress gene expression epigenetically⁸. This raises the possibility that loss of BCOR function, due to acquired mutations in its gene, may contribute to an altered epigenetic landscape in RB1-deficient retinal cells. Consequently, inappropriate expression of crucial genes may impair cell maturation and so facilitate the progression of retinoblastoma. It will be of interest to determine whether BCOR is part of the repression machinery that silences SYK expression in the normal retina, and whether acquired *BCOR* mutations provide at least one route to altered expression of SYK in retinoblastoma.

Nevertheless, the current work — using a comprehensive, integrated genomics approach — is notable not just for demonstrating that epigenetic alterations have a predominant role in the progression of retinoblastoma. The new possibilities it raises for therapies in this childhood malignancy, and possibly in other types of tumour, are equally noteworthy.

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