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Oncogenic defects do not usually induce total chaos in a cell, but instead make subtle alterations. In an article on page 649, Oliver Sieber, Simon Tomlinson and Ian Tomlinson discuss how cells must acquire several functional defects that are neither too weak nor too strong, but, rather, lie within a 'permissive window' that allows tumours to form. This window is determined by several factors, including the cancer-cell environment, and could explain why even the most well-known cancer genes are only mutated in certain tumour types.

So what are some of these 'subtle' cancer genes? On page 603, Robert Benezra and colleagues describe how the inhibitor of DNA-binding (Id) proteins mediate several oncogenic pathways. Although no mutations in these proteins have been found in tumour samples, Ids are overexpressed in some tumour types, which might help push cells towards de-differentiation, unrestricted proliferation and neoangiogenesis.

The cancer/testis antigens are not outright oncoproteins, but they represent another protein family that is upregulated in some tumours. Simpson *et al.* (page 615) describe how, despite being studied for decades and used as cancer vaccine targets, the functions of gametogenic proteins in transformed somatic cells are still unclear. Also, germline mutations in the *TCL1* (T-cell leukaemia/lymphoma) genes, normally expressed only during embryogenesis, lead only to specific types of lymphoid malignancies, as discussed by Michael Teitell (page 640).

Transcription-profiling studies indicate that hundreds of changes in levels of gene expression occur in different tumour types, so we have only just begun to identify these subtle oncogenes. Eventually, however, we might piece together how a combination of specific genetic alterations, determined by cell type and environment, can lead to cancer.


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