TUMORIGENESIS

Better by half

Recent cancer genome screens have shown that cancers have specific regions of hemizygous deletion that are likely to affect several genes. Research by Nicole Solimini, Stephen Elledge and colleagues indicates that these regions contain more genes that suppress tumour growth and fewer genes that are essential for cell survival and proliferation.

Initially, the authors investigated whether a list of known tumour suppressor genes (TSGs) from the Cancer Gene Census and genes that the authors had identified as undergoing homozygous loss-of-function mutations in 526 tumours from the COSMIC database were present in recurrent hemizygous deletions. Only 18 of 82 recurrent deletions were found to contain a known or a putative TSG. So, what other genes are present in these regions? The authors reasoned that genes that regulate proliferation are likely to have a big impact on cancer cell fitness, so they set up a short hairpin RNA (shRNA) screen for suppressors of tumorigenesis and/or proliferation (STOP) genes and growth enhancers and oncogenes (GO) genes in human mammary

epithelial cells. By combining data from a primary screen and validation screens, the authors identified 878 STOP genes that increase proliferation more than fourfold when targeted by four independent shRNAs. The chromosomal location of these genes was then mapped relative to deletions from 3,131 tumours, and this revealed a significant enrichment of STOP genes (451) in recurrent deletions, with only six of the genes being proven TSGs.

If hemizygous loss of multiple STOP genes increases cancer cell fitness through cumulative haploinsufficiency, then one assumes that the loss of GO genes in these regions would be minimized. The authors used both *in silico* analyses and shRNA screens to identify GO genes and whether they localize to regions of recurrent hemizygosity. Their results indicate that recurrent hemizygous deletions exist in

chromosomal regions that have unusually low levels of GO genes.

So, recurrent regions of somatic hemizygosity might exist in tumours because they enable a reduction in the expression levels of genes that restrict cell proliferation and survival, and minimize the loss of genes that are essential for cell survival, leading the authors to suggest a 'cancer gene islands model' of cancer evolution. They speculate that if the loss of multiple STOP genes results in phenotypes on which natural selection acts during tumour progression, then regions of recurrent amplification might contain multiple genes, the increased dosage of which promotes proliferation and survival.

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Lara Crow/NPG