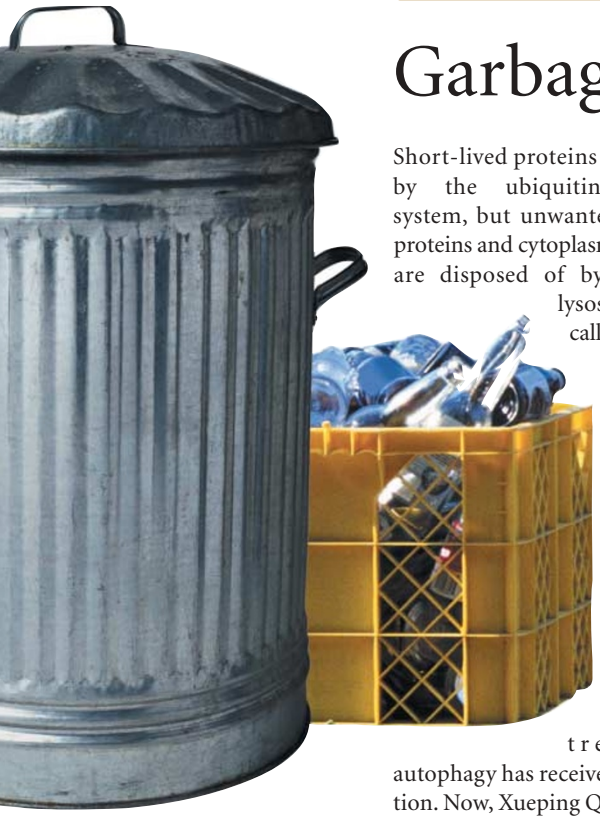

TUMOUR SUPPRESSORS

Garbage disposal

Short-lived proteins are degraded by the ubiquitin–proteasome system, but unwanted long-lived proteins and cytoplasmic organelles are disposed of by a dynamic lysosomal process called autophagy. Although ubiquitin–proteasome proteo-lysis has been shown to contribute to tumorigenesis and has been the target of developing anticancer treatments, autophagy has received little attention. Now, Xueping Qu *et al.* report that the Beclin 1 (*Becn1*) autophagy gene is a haploinsufficient tumour suppressor, which contributes to cancer pathogenesis.

BECN1 is monoallelically deleted in up to 75% of ovarian cancers, 50% of breast cancers and 40% of prostate cancers. However, biallelic inactivations have not been found, so it is not a classic tumour-suppressor gene. To establish whether the monoallelic deletion of *Becn1* contributes to tumorigenesis, Qu and colleagues generated $Becn1^{+/-}$ mice and examined spontaneous tumour development in the mice, which were sacrificed at 13–18 months. 15% of the $Becn1^{+/-}$ mice had palpable tumours and 30% had microscopic tumours, compared with only 1% and 14% of $Becn1^{+/+}$ mice, respectively. The main tumour types that were seen in the $Becn1^{+/-}$ mice were lung cancers, liver cancers and lymphomas. Interestingly, these are different from the tumour types that are associated with *BECN1* heterozygosity in humans. All the tumours in the $Becn1^{+/-}$ mice expressed Becn1 protein, and Southern blot analysis showed that there were no mutations in the wild-type allele. In a mouse model that is prone to development of hepatocellular carcinoma, deletion of one allele of *Becn1* led to earlier development of liver dysplasia.

But what is the role of *Becn1* monoallelic deletion in cell growth control and autophagy? $Becn1^{+/-}$ mice developed mammary-gland intraepithelial neoplasia by 13–18 months and the authors showed that the developing mammary glands in mice that were 5-weeks old already had increased cell proliferation and increased DNA synthesis, but no change in the levels of apoptosis. Furthermore, autophagy — as measured by electron-microscopy analysis and expression of a marker of autophagy, GFP-LC3 — was decreased in the main

TUMOUR SUPPRESSORS

The protective effect of arrest

That the apoptotic function of p53 protects cells from tumorigenesis has long been known, but what part does cell-cycle arrest have in the tumour-suppressive arsenal of p53? Guillermina Lozano and colleagues report in the January issue of *Nature Genetics* that the checkpoint function of p53 might be important for preserving genomic stability and, therefore, for suppressing tumorigenesis.

A *TP53* point mutation has been found in human tumours that results in a protein that is unable to induce apoptosis, but is still able to induce arrest. The authors generated mice that were homozygous for an equivalent mutation: a guanine to cytosine mutation in base 515 of *Trp53* — $Trp53^{515C/515C}$ — which corresponds to an arginine to proline amino-acid substitution at residue 172. They isolated mouse embryonic fibroblasts (MEFs) from these mice and treated them with γ-radiation. The $Trp53^{515C/515C}$ MEFs were better able to arrest than *Trp53*-null MEFs following γ-radiation, but did not arrest as effectively as wild-type MEFs. The extent of cell-cycle arrest correlated with the ability to induce expression of the cyclin-dependent kinase inhibitor Waf1.

As expected, the $Trp53^{515C/515C}$ MEFs were resistant to apoptosis that was induced by various conditions — exposure to doxorubicin and serum deprivation. $Trp53^{515C/515C}$ thymocytes were also resistant to apoptosis that was induced by γ-radiation, but were sensitive to apoptosis that was induced by dexamethasone, which operates through a p53-independent pathway.

So, what effect does this mutation have on the ability of p53 to protect cells from tumorigenesis? Whereas 90% of *Trp53*-null mice had developed tumours by 7 months, only 15% of $Trp53^{515C/515C}$ mice had succumbed to tumorigenesis. The $Trp53^{515C/515C}$ mice eventually developed lymphomas and sarcomas, but these were of a different type to those in the *Trp53*-null mice and are thought to have arisen through a different mechanism.

Apoptosis was detected at low levels in tumours from both *Trp53*-null and $Trp53^{515C/515C}$ mice, so what could account for the difference in tumour type and latency? Loss of p53 characteristically results in highly aneuploid cells, but this was not found to be the case in the $Trp53^{515C/515C}$ cells — they tended to be diploid or tetraploid. Genome stability therefore seems to protect against early-onset tumorigenesis. The mechanism by which p53 suppresses aneuploidy is thought to be by controlling centrosome duplication — more than 50% of *Trp53*-null MEFs frequently contained three or more centrosomes, whereas 85% of $Trp53^{515C/515C}$ MEFs contained just two.

So, although the ability of p53 to induce apoptosis is important for preventing tumorigenesis, it is not the only mechanism that matters. The prevention of genome instability — possibly by inducing cell-cycle arrest — also has a significant protective effect.

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References and links

ORIGINAL RESEARCH PAPER Liu, G. *et al.* Chromosome stability, in the absence of apoptosis, is critical for suppression of tumorigenesis in *Trp53* mutant mice. *Nature Genet.* **36**, 63–68 (2004)

FURTHER READING Vousden, K. H. & Lu, X. Live or let die: the cell's response to p53. *Nature Rev. Cancer* **2**, 594–604 (2002)

WEB SITE

Guillermina Lozano's lab: http://gsbs.gs.uth.tmc.edu/tutorial/lozano.html