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TUMOUR SUPPRESSORS

The dark side of p27

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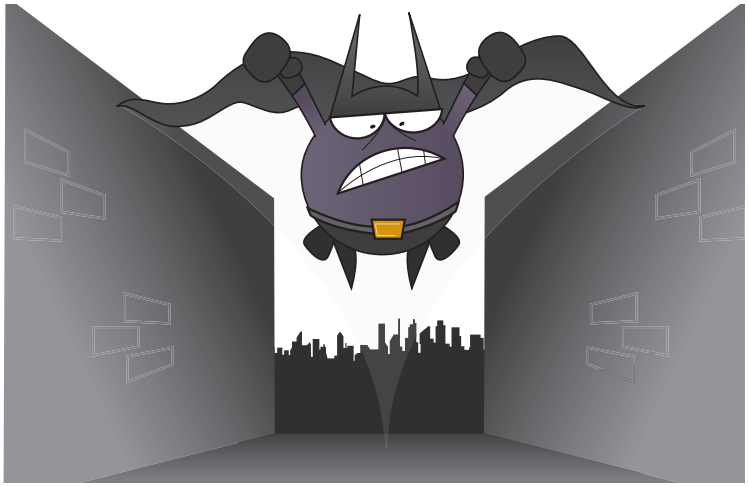
URLs
CDKN1B



Several pieces of evidence indicate that the tumour suppressor p27 (encoded by *CDKN1B*) has other functions beyond its role as a cell-cycle inhibitor. James Roberts, Arnaud Besson and colleagues now show that, unexpectedly, p27 can behave as a dominant oncoprotein *in vivo*.

To study p27 function independent of its cell-cycle regulatory activity, the authors generated a knock-in mouse expressing a p27 mutant ($p27^{CK^-}$) in which four amino-acid replacements impair its ability to bind and inhibit cyclin–cyclin-dependent kinase (CDK) complexes. Similar to p27-null mice, $p27^{CK^-/CK^-}$ mice have an increased body size and organomegaly, features that underline the importance of p27 in cell-cycle regulation. But in contrast to p27-null mice, which only develop pituitary tumours, $p27^{CK^-/CK^-}$ mice (from two different genetic backgrounds) had a high incidence of hyperplastic lesions and spontaneous tumours in multiple tissues. Most mutant mice developed pituitary tumours, which were larger, more vascularized and more aggressive than those previously observed in p27-null mice, and caused death at an earlier age.

The oncogenic effect of the $p27^{CK^-}$ mutant is genetically dominant given that $p27^{+/CK^-}$ heterozygous mice develop hyperplastic and neoplastic lesions — although with a delayed onset compared with $p27^{CK^-/CK^-}$ homozygous mice — and genotyping of eight lung tumours from $p27^{+/CK^-}$ mice did not show loss of heterozigosity in the wild-type allele.

So, why is $p27^{CK^-}$ oncogenic? Interestingly, the $p27^{CK^-}$ mutation caused retinal dysplasia owing to an abnormal proliferation of retinal progenitor cells. In addition, $p27^{CK^-}$ induced an age-dependent increase of the bronchioalveolar stem cell pool that was linked to the progression from lung dysplasia to tumour development. These data indicate that the oncogenic function of p27 is associated with inappropriate proliferation of stem and progenitor cells.

By dissecting p27 function *in vivo*, these authors have uncovered a new, unforeseen, oncogenic activity of p27 that seems to be independent of CDK inhibition and might require cytoplasmic as well as nuclear activity. This might explain why homozygous inactivation of *CDKN1B* (by mutation or silencing) is extremely rare in human tumours.

Francesca Pentimalli

ORIGINAL RESEARCH PAPER Besson, A. *et al.* Discovery of an oncogenic activity in $p27^{Kip1}$ that causes stem cell expansion and a multiple tumour phenotype. *Genes Dev.* **21**, 1731–1746 (2007)