IN BRIEF

TELOMERES

A highly selective telomerase inhibitor limiting cancer cell proliferation.

Damm, K. *et al. EMBO J.* **20**, 6958–6658 (2001)

Telomerase — the enzyme responsible for telomere maintenance and hence replicative potential — is expressed in most human cancers, but not in normal somatic tissue, making it a good candidate for anticancer therapy. Damm *et al.* have identified several compounds that inhibit telomerase, resulting in telomere shortening. One of these, BIBR1532, also limits the tumorigenic potential of tumour cells in a mouse xenograft model, without serious side effects.

MOUSE MODELS

Analysis of lung tumor initiation and progression using conditional expression of oncogenic *K-ras.*

Jackson, E. L. *et al. Genes Dev.* **15**, 3243–3248 (2001)

Induction and apoptotic regression of lung adenocarcinomas by regulation of a *K-Ras* transgene in the presence and absence of tumor suppressor genes.

Fisher, G. H. *et al. Genes Dev.* **15**, 3249–3262 (2001)

Oncogenic *KRAS* mutations can give rise to lung adenocarcinomas, but where do these tumours arise, and is *KRAS* also important for tumour maintenance? Two new mouse models address these questions. Jackson and colleagues can switch on oncogenic *Kras* in a few cells by administering a low dose of an adenoviral vector encoding an enzyme that edits a stop codon out of an engineered *Kras* gene. This has allowed them to identify a progenitor-like cell as the cell of origin for lung adenocarcinoma. Fisher and colleagues can switch *Kras* on and off at will by adding or removing doxycycline from the diet of the mice. In this model, tumours regress rapidly by apoptosis when *Kras* expression is switched off, even in the absence of p53, Ink4a or Arf. This has implications for therapy as it indicates that blocking the RAS pathway, even in advanced tumours, could lead to apoptosis of tumour cells.

STRUCTURAL BIOLOGY

A novel pH-dependent destabilization of a mutant p53 tetramer leads to tumorigenesis.

DiGiammarino, E. L. *et al. Nature Struct. Biol.* **9**, 12–16 (2002)

These authors undertook a structural analysis of a mutant form of p53 isolated from children in southern Brazil who have a high incidence of adrenocortical carcinoma. This mutant p53 contains an Arg-to-His mutation at amino acid 337 in the tetramerization domain, causing p53 to lose stability and become highly pH sensitive. The authors propose that the elevated pH in the developing adrenal gland might destabilize p53 and cause it to lose its tumour-suppressor function, leading to adrenocortical cancer.

ANGIOGENESIS

What's going on?

Adhesion molecules such as integrins allow cells to transmit signals from the extracellular matrix (ECM), and have been implicated in tumour growth and angiogenesis. Several studies have reported that integrin inhibitors prevent tumour growth and angiogenesis in mice, and one inhibitor — vitaxin — is now being tested in cancer clinical trials. But a surprising article in the January issue of *Nature Medicine* reports a contradictory finding — that tumour growth is actually enhanced in mice lacking β3 and β5 integrins.

Integrins are a family of heterodimeric transmembrane receptors that consist of an α and β subunit that each recognize a unique set of ECM ligands. Blockade of αvβ3 or αvβ5 integrins with monoclonal antibodies or small-molecule inhibitors prevent tumour growth and angiogenesis in animal models. Conversely, previous knockout studies have reported that mice lacking αv, β3 or β5 integrins undergo normal developmental angiogenesis. The *Nature Medicine* study by Reynolds *et al.* adds to these results, showing that tumour-induced angiogenesis also occurs, and is actually enhanced, in β3-deficient and β3/β5 double knockout mice. Furthermore, tumours grow faster in the knockout mice. So the authors conclude that neither β3 nor β5 integrins are essential for neovascular formation.

But what could explain the differences between blocking agents and knockout models? One possibility is that in the knockout mice, other adhesion proteins are overexpressed in compensation. Reynolds *et al.* did not detect increased levels or activities of other integrins, although upregulation of other adhesion proteins could not be ruled out. A second possibility is that the integrin antagonists could indirectly inhibit the function of other integrins or other cell-surface molecules. A third possibility is that the integrin-null mice undergo an abnormal mechanism of angiogenesis.

The authors conclude, however, that rather than being required for angiogenesis, integrins αvβ3 and αvβ5 might normally function to limit it. They observed that expression of the vascular endothelial growth factor receptor-2 (VEGFR-2) was increased in endothelial cells of integrin knockout mice, which could promote angiogenesis. Transfection of β3-null endothelial cells with the gene encoding β3 integrin reduced the expression of VEGFR-2 to wild-type levels, indicating that β3 integrin signalling downregulates VEGFR-2 expression. Reynolds *et al.* propose that integrin inhibitors might dysrgulate this pathway, although they don't explain how. Although the authors do not dispute the efficacy of αvβ3 antagonists in preventing angiogenesis or their potential as anticancer drugs, they state that a more thorough understanding of the mechanisms of action of these inhibitors and the roles of integrins in angiogenesis is required.

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References and links

ORIGINAL RESEARCH PAPER Reynolds, A. *et al.* Enhanced pathological angiogenesis in mice lacking β3 integrin or β3 and β5 integrins. *Nature Med.* **8**, 27–34 (2002)
FURTHER READING Eliceiri, B. P. & Cheresh, D. A. The role of αv integrins during angiogenesis: insights into potential mechanisms of action and clinical development. *J. Clin. Invest.* **103**, 1227–1230 (1999)
WEB SITE
Kairbaan M. Hodivala-Dilke's lab: http://www.icnet.uk/lis/ipub/brochure/xchodi.pdf