VHL exists as two isoforms: the longer VHL_{30} isoform and the shorter VHL_{19} isoform that results from internal initiation at methionine 54. By raising antibodies that are specific for each isoform, Krek and colleagues revealed that, whereas the shorter isoform localizes predominantly to the nucleus, the longer VHL_{30} isoform co-localizes with the cytoplasmic microtubule network and depends on an intact microtubule network for this.

To address the functional significance of this localization, the authors tested the effect of VHL binding on microtubule dynamics and found that it mediates microtubule stabilization, protecting microtubules against nocodazole treatment. One important distinction is that this function of VHL seems to be independent of its ability to form an active E3 ligase complex. So what is the relevance, if any, of this role to the tumour-suppressor function of VHL? To test this, the authors looked at the effects of different *VHL* mutations associated with each disease subtype on microtubule stabilization. Intriguingly, only mutations associated with type 2A VHL disease (and one associated with type 2C disease), which is characterized by a high risk of developing adrenal-gland tumours and cerebellar haemangioblastomas, were abrogated in microtubule stabilization.

How this function of VHL might contribute to tumour development remains to be seen, but from this work a new model for VHL function is beginning to emerge. The authors propose that each of the two VHL isoforms has a distinct role. Whereas the shorter isoform resides in the nucleus and is required as part of an E3 ligase complex to regulate HIF under normoxic conditions, the longer isoform has a novel E3-independent function in the cytoplasm, mediating microtubule stability. Exactly how loss of microtubule stabilization by VHL contributes to tumour progression remains to be seen.

Alison Schuldt

Associate Editor, Nature Cell Biology

References and links

ORIGINAL RESEARCH PAPER Hergovich, A. *et al.* Regulation of microtubule stability by the von Hippel–Lindau tumour suppressor protein pVHL. *Nature Cell Biology* **5**, 64–70 (2003)

FURTHER READING Kaelin, W. G. Jr. Molecular basis of the VHL hereditary cancer syndrome. *Nature Rev. Cancer* **2**, 673–682 (2002)

throughout the blood vessels and lymphatic system.

Golub and colleagues admit that although their outcome predictor was statistically significant, it was still imperfect, and suggest that additional factors are involved in determining tumour behaviour. But the discovery of an expression signature that can be used to classify a subset of primary solid tumours as premetastatic will be useful not only in determining prognosis, but also in designing therapies to stop the spread of tumours.

Kristine Novak

References and links

ORIGINAL RESEARCH PAPER Ramaswamy, S., Ross, K. N., Lander, E. S. & Golub, T. A molecular signature of metastasis in primary solid tumours. *Nature Genet.* **33**, 49–54 (2003)

FURTHER READING Ramaswamy, S. & Golub, T. R. DNA microarrays in clinical oncology. *J. Clin. Oncol.* **20**, 1932–1941 (2002)

WEB SITE

Todd Golub's web site: http://www-genome.wi.mit.edu/cancer/

IN BRIEF

ONCOGENES

High frequency of *BRAF* mutations in nevi.

Pollock, P. M. *et al*. *Nature Genet*. 25 Nov 2002 (doi:10.1038/ng1054)

BRAF encodes an oncogenic kinase that is involved in the RAS–RAF–MAPK signalling pathway. Earlier this year, *BRAF* was found to be mutated in malignant melanoma, but how early in the transformation process does this occur? Pollock *et al.* now show that mutations in *BRAF* occur very early in melanoma pathogenesis — at the nevi stage. Some 82% of nevi had an activating mutation in *BRAF*, resulting in the amino-acid substitution V599E, indicating that this is a crucial step in the initiation of melanoma.

CHECKPOINTS

53BP1 functions in an ATM-dependent checkpoint pathway that is constitutively activated in human cancer.

DiTullio, R. A. *et al. Nature Cell Biol.* **4**, 998–1002 (2002)

53BP1 localizes to double-strand breaks following irradiation, indicating that it might be a checkpoint protein. RNAi of 53BP1 showed that it is required for the ATM-dependent phosphorylation of certain substrates after DNA damage, and for the G2–M checkpoint. Interestingly, in several cancer cell lines that have mutant *TP53*, 53BP1 foci form even in the absence of irradiation, which has led the authors to suggest that an activated checkpoint pathway might provide a selective pressure for mutation of *TP53*.

TUMORIGENESIS

Highly penetrant, rapid tumorigenesis through conditional inversion of the tumor suppressor gene *Snf5*.

Roberts, C. W. M. *et al. Cancer Cell* **2**, 415–425 (2002)

The SWI/SNF chromatin remodelling complex might act as a tumour suppressor, but definitive evidence has been lacking. Now, a reversible inactivating conditional allele of *Snf5* — a core subunit of SWI/SNF — has been generated to investigate this. Inactivation of *Snf5* results in the formation of tumours — T-cell lymphomas and rare rhaboid tumours — in 100% of mice with an average latency of 11 weeks, confirming that it does act as a tumour suppressor.

THERAPEUTICS

Using cyclooxygenase-2 inhibitors as molecular platforms to develop a new class of apoptosis-inducing agents.

Zhu, J. *et al. J. Natl Cancer Inst.* **94**, 1745–1757 (2002)

COX2 inhibitors act as chemopreventive drugs by sensitizing cancer cells to apoptosis, but why do agents that inhibit COX2 to a similar extent show different potencies against cancer cells? A systematic chemical approach to modify the structures of celecoxib and rofecoxib was used to generate compounds that could be tested for their ability to induce apoptosis of prostate cancer cells. The structural requirements for COX2 inhibition are different from those for apoptotic induction — which occurs by downregulating AKT and ERK2 — so existing COX2 inhibitors could be modified to maximize their ability to kill cancer cells.