IN BRIEF

CANCER GENETICS

HIF overexpression correlates with biallelic loss of fumerate hydratase in renal cancer: novel role of fumerate in regulation of HIF stability.

Isaacs, J. S. *et al*. *Cancer Cell* **8**, 143–153 (2005)

Fumerate hydratase (FH) converts fumerate to malate. This paper shows that increased levels of fumerate function as a competitive inhibitor of the prolyl hydroxylase that labels hypoxia-inducible factor (HIF) for degradation by the von Hippel–Lindau (VHL)-containing ubiquitin-ligase complex. Increased levels of fumerate do not affect VHL function, so the development of renal tumours in patients with familial *FH* mutations is HIF-dependent, but VHL-independent.

APOPTOSIS

Clusterin inhibits apoptosis by interacting with activated Bax.

Zhang, H. *et al*. *Nature Cell Biol.* 21st August (doi:10.1038/ncb1291)

This paper shows that the glycoprotein clusterin inhibits the pro-apoptotic protein BAX. In response to chemotherapeutic drugs, BAX undergoes a conformational change into an active form, but clusterin prevents oligomerization of activated BAX, which is essential for its pro-apoptotic function. Consequently, clusterin can promote MYC-induced transformation by inhibiting MYC-induced apoptosis, demonstrating that clusterin is a valid anticancer target.

TUMORIGENESIS

Evasion of the p53 tumour surveillance network by tumour-derived *MYC* mutants.

Hemann, M. T. *et al*. *Nature* **436**, 807–811 (2005)

Two common mutant *MYC* alleles found in human Burkitt lymphoma uncouple the capacity of MYC to induce both apoptosis and proliferation. The mutant MYC proteins activate proliferation and still activate p53 by triggering the activation of ARF, but unlike wild-type MYC, do not induce activation of the BH3-only, pro-apoptotic protein BIM. So, parallel apoptotic pathways function to suppress MYC-induced transformation and disabling a p53-independent apoptosis pathway is enough for tumour cells to evade p53 action.

THERAPEUTICS

Efficient delivery of small interfering RNA to bone-metastatic tumors by using atelocollagen *in vivo*.

Takeshita, F. *et al*. *Proc. Natl Acad. Sci. USA* 9 Aug (doi: 10.1073/pnas.0501753102)

The expression of genes involved in certain cancers can be reduced by treatment with short interfering RNAs (siRNAs), but unwanted immune reactions have hindered delivery strategies. This paper shows that siRNAs function successfully in mice when delivered on modified collagen molecules rather than viral or lipid vectors. When targeted against a bioluminescence marker there was a 90% decrease in luminescence; when targeted against two prostate cancer genes, tumour growth was reduced throughout the body.

MITOSIS

Motoring ahead

Agents that target the mitotic spindle to disrupt cell division, such as taxanes and vinca-alkaloids, are widely used as anticancer drugs. As these drugs target microtubules, which have a wide variety of functions in non-mitotic cells, they also have a number of side effects. Weikang Tao and colleagues have investigated another component of the mitotic spindle, the KSP motor protein, which only functions during mitosis, and showed that KSP inhibitors have a unique mechanism of inducing cancer cell apoptosis.

KSP, a member of the kinesin superfamily, mediates centrosome separation and formation of the bipolar mitotic spindle during mitosis. Disruption of this process leads to activation of a 'spindle assembly checkpoint' that prevents the onset of anaphase and results in cell-cycle arrest. KSP inhibitors are therefore being developed as a new generation of antimitotic agents.

Tao *et al.* performed a high-throughput screen to identify inhibitors of the motor domain of KSP. They discovered a compound, which they named KSP-IA, and showed it to be a specific and cell-permeable small molecule inhibitor of the enzymatic activity of KSP. In ovarian and colon cancer cell lines, KSP-IA activated the spindle checkpoint, leading to mitotic arrest. These effects were reversible — after removal of the drug, cells underwent normal chromosome segregation and cytokinesis. Extending the time of drug treatment to beyond 24 hours, however, caused a significant fraction of cells to undergo apoptosis.

How might disruption of mitotic-spindle function lead to apoptosis? The authors found that in spindle-checkpoint-competent cells, apoptosis induction by prolonged exposure to this drug was coupled with 'mitotic slippage' — a process by which cells, in the presence of persistent spindle damage, override the spindle checkpoint to exit mitosis and form tetraploid cells. A combination of spindle-checkpoint activation followed by mitotic slippage activates the pro-apoptotic protein BAX, mediating the mechanism of cell-death induction in KSP-IA treated cells.

These findings indicate that mitotic slippage, after activation of the spindle checkpoint, increases the lethality of KSP inhibitors. This is similar to the mechanisms of the DNA-damage checkpoint, and has important implications for the development of KSP inhibitors as anticancer drugs.

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References and links

ORIGINAL RESEARCH PAPER Tao, W. *et al*. Induction of apoptosis by an inhibitor of the mitotic kinesin KSP requires both activation of the spindle assembly checkpoint and mitotic slippage. *Cancer Cell* **8**, 49–58 (2005)