IN BRIEF

GENETICS

Trp53^{R172H} and *Kras*^{G12D} cooperate to promote chromosomal instability and widely metastatic pancreatic ductal adenocarcinoma in mice.

Hingorani, S. R. *et al. Cancer Cell* **7**, 469–483 (2005)

Through endogenous expression of *Trp53*^{R172H} and *Kras*^{G12D} in the mouse pancreas, Hingorani *et al.* created a mouse model of pancreatic ductal adenocarcinoma that recapitulates the human disease. The primary carcinomas and metastases have a high degree of genomic instability, but no mutations were observed in several well-known tumour-suppressor gene pathways. This indicates that distinct genetic pathways lead to the formation of these tumours.

FREE RADICALS

Nitric oxide synthase II suppresses the growth and metastasis of human cancer regardless of its up-regulation of protumor factors.

Le, X. *et al. Proc. Natl Acad. Sci. USA* 6 June 2005 (doi:10.1073/pnas.0409581102)

Le *et al.* report that in different human tumour cell types expressing inducible nitric oxide (NO) synthase II, production of NO leads to upregulation of multiple angiogenic molecules. However, the NO-producing tumour cells did not form tumours or metastases in mouse models, owing to NO-mediated apoptosis. The authors conclude that NO has a dose-dependent antitumour activity, in spite of its ability to upregulate pro-angiogenic factors.

METASTASIS

Claudin-1 regulates cellular transformation and metastatic behavior in colon cancer.

Dhawan, P. *et al. J. Clin. Invest*. 16 June 2005 (doi:10.1172/JCI24543)

Disruption of tight junctions between cells is associated with tumour-cell invasion and metastasis. Dhawan *et al.* report increased expression of the tight junction protein claudin-1 in human primary colon carcinomas and metastases, along with mislocalization of this protein from the cell membrane to the cytoplasm and nucleus. Overexpression of claudin-1 promotes cellular transformation and invasive behaviour, whereas siRNA-mediated inhibition decreased the tumorigenic and metastatic potential of colorectal cancer cells.

PROTEIN KINASES

A screen of the complete protein kinase gene family identifies diverse patterns of somatic mutations in human breast cancer.

Stephens, P. *et al. Nature Genet.* **37**, 590–592 (2005)

To explore the mutational landscape in breast cancer genomes, Stratton and colleagues sequenced the coding regions of 518 protein kinases in tumours. Somatic mutations were distributed unevenly among the cancers examined. Whereas twelve primary breast cancers had no somatic mutations, two had a single mutation each and one had two mutations, one cancer had 52 mutations, all of which were base substitutions. The authors discuss how such mutations might arise and contribute to cancer development.

STRUCTURAL BIOLOGY

Spirals and curls

Vinblastine has been used to treat cancer for decades, but although it is known to target tubulin, its binding site and mechanism of action has only now been shown. Marcel Knossow and colleagues have elucidated the X-ray structure of vinblastine bound to tubulin, which explains how vinblastine induces spiralling in microtubules and leads to mitotic block.

The authors incubated vinblastine with a complex of two tubulin heterodimers, each consisting of an α- and a β-subunit, bound by the RB3 protein stathmin-like domain, which is involved in the regulation of microtubule dynamics. They determined that there is one vinblastine-binding site at the interface between the two tubulin molecules and that vinblastine binds to the α-subunit of one molecule and the β-subunit of the other molecule. Other tubulin-binding molecules, such as paclitaxel and colchicine, bind to just one tubulin molecule. Further analysis revealed that the vinblastine site consists of residues that are involved in longitudinal protofilament contacts. Vinblastine buries 80% of its surface area in the complex and leads to a conformational change in the tubulin. The D′ ring of vinblastine is part of the drug that binds to tubulin, and this explains previous observations that modification of the D′ ring affects drug activity. Studies exploiting the changes in fluorescence that occur on binding of vinblastine to the tubulin complex showed that binding occurs in two stages: formation of a rapid equilibrium collision complex followed by a slower rearrangement that might coincide with the changes in the structure.

These data provide insight into how vinblastine binding affects tubulin dynamics. Vinblastine induces the formation of spiral-like tubulin aggregates and the authors deduce from this and their new structural data that, in these aggregates, vinblastine crosslinks the α-subunit of one molecule with the β-subunit of another molecule. It has also been previously observed that vinblastine binds to microtubule tips and at low concentrations suppresses the dynamic instability of polymerizing ends, probably leading to the mitotic block that results in the death of tumour cells in the clinic. Knossow and colleagues suggest that at low concentrations vinblastine causes the microtubule end to curve, but leaves the core of the microtubule intact. At high concentrations, vinblastine has been shown to cause protofilament spirals and depolymerize microtubules. The authors propose that, in this scenario, vinblastine causes more curving all the way along the microtubules, so more microtubule-specific contacts are lost, triggering microtubule disassembly and mitotic block.

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References and links

ORIGINAL RESEARCH PAPER Gigant, B. *et al.* Structural basis for the regulation of tubulin by vinblastine. *Nature* **435**, 519–522 (2005)
FURTHER READING Jordan, M. A. & Wilson, L. Microtubules as a target for anticancer drugs. *Nature Rev. Cancer* **4**, 253–265 (2004)