IN BRIEF

GENETICS

CDX2 polymorphisms, RNA expression, and risk of colon cancer.

Rozek, L. S. *et al. Cancer Res.* **65**, 5488–5492 (2005)

The intestinal-epithelial-cell transcription factor CDX2 is often downregulated in colorectal cancer. But epidemiological and gene-expression data analysed in this study did not implicate common *CDX2* variants in susceptibility to this disease. *CDX2* expression levels did, however, correlate with microsatellite instability and tumour location, indicating a role for CDX2 in the specification of human gastrointestinal cell fate.

CELL CYCLE

CDK inhibitors uncouple cell cycle progression from mitochondrial apoptotic functions in DNA-damaged cancer cells.

Le, H. V., *et al. J. Biol. Chem.* 6 July 2005 (doi:10/1047/jbc.M504689200)

The efficacy of DNA-damaging anticancer agents is severely reduced if cancer cells avoid apoptosis and, instead, enter cell-cycle arrest. The results presented here help clarify the relationship between cell-cycle progression and apoptosis during therapeutic responses, and have important implications for the effective therapeutic combination of agents that affect the cell cycle with agents that cause DNA damage.

STEM CELLS

Identification of bronchioalveolar stem cells in normal lung and lung cancer.

Kim, C. F. B. *et al. Cell* **121**, 823–835 (2005)

A stem-cell population that has been identified and isolated from the lung represents a possible target for the fight against some lung cancers. The research group, led by Tyler Jacks, called these cells bronchioalveolar stem cells (BASCs), after their location in the bronchioalveolar duct junction. Not only do BASCs have self-renewal and multipotent properties, they also proliferate in response to oncogenic K-RAS, both *in vitro* and *in vivo*. The authors conclude that the transformation of BASCs might give rise to adenocarcinomas.

CHEMOTHERAPY

The optimal biological dose of metronomic chemotherapy regimens is associated with maximum antiangiogenic activity.

Shaked, Y. *et al. Blood* 5 July 2005 (doi: 10.1182/blood-2005-04-1422)

The remarkable efficacy of 'metronomic' chemotherapy — in which therapy is given regularly and frequently in low, non-toxic doses — is thought to be due to its anti-angiogenic effects. This has now been verified by Shaked *et al.*, who have also identified a possible new assay for determining the 'optimal biological dose' (OBD) of metronomic chemotherapy. They found that the OBD in several preclinical tumour models correlated well with the number of circulating peripheral blood endothelial precursors that express vascular endothelial growth factor receptor 2.

TECHNOLOGY

Gene hunters

Despite the fact that lung cancer is the leading cause of cancer mortality worldwide, few genetic defects have been found to mediate its pathogenesis. Using a combination of high-resolution comparative genome hybridization (CGH) and gene-expression profiling, Ron DePinho and colleagues have now identified several loci with candidate oncogenes.

Non-small cell lung cancer (NSCLC) accounts for over 75% of lung cancer cases, with adenocarcinoma and squamous cell carcinoma (SCC) being the most common subtypes. DePinho and colleagues attempted to define the genetic basis of these tumour types by first identifying regions of recurring chromosome gain and loss in tumour samples, and then associating these chromosomal aberrations with copy-number driven alterations in gene expression.

In comparing tumour subtypes of 44 NSCLC samples, they found that the chromosome region 3q26–29 was the only copy number alteration specific to the SCC subtype. This locus had also previously been reported to be amplified in SCC of the head and neck. So which genes in this region might contribute to SCC pathogenesis? The authors observed that p63, a known regulator of squamous cell differentiation, is at this locus and is overexpressed only in SCC samples. Mice that overexpress this gene develop severe squamous metaplasia, so p63 is a good candidate for an SCC oncogene.

Other than the amplification of the chromosome-3 region, there were no major differences observed between the NSCLC subtypes, indicating that adenocarcinomas and SCCs might arise from a common lung stem cell or precursor cell. DePinho also compared the NSCLC dataset with other recently published CGH datasets, and found that two amplicons, at 8p12 and 20q11, were common to both NSCLC and pancreatic ductal adenocarcinoma. Genes in these regions that were amplified and overexpressed in tumour samples included *WHSC1L1*, which had been previously observed to be amplified in breast cancer, and *TPX2*, which regulates Aurora-A function at the spindle checkpoint. This technology has therefore yielded important new candidates for the genetic basis of lung cancers.

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References and links

ORIGINAL RESEARCH PAPER Tonon, G. *et al.* High-resolution genomic profiles of human lung cancer. *Proc. Natl Acad. Sci. USA* **102**, 9625–9630 (2005)