IN BRIEF

GENETICS

Beckwith–Wiedemann syndrome and IVF: a case control study.

Halliday, J. *et al. Am. J. Hum. Genet.* **75**, 526–528 (2004)

Recent studies have indicated a link between *in vitro* fertilization (IVF) and imprinting disorders that are associated with an increased risk of childhood tumours. In this case–control study, Halliday and colleagues found that in the IVF population they assessed, the risk of having a child with Beckwith–Wiedemann syndrome (BWS) was nine times greater than in the general population. Interestingly, IVF BWS patients consistently show hypomethylation of the *KVDMR1/LIT1* locus, compared with ~46% of all BWS cases. This finding has important implications for BWS and childhood cancer development.

BREAST CANCER

Phenotypic conversion of human mammary carcinoma cells by autocrine human growth hormone.

Mukhina, S. *et al. Proc. Natl Acad. Sci. USA* 7 Sept 2004 (doi:10.1073/pnas.0405881101)

Increased human growth hormone (HGH) levels are associated with a metastatic phenotype in mammary carcinoma cells, but whether they have a causal role in metastasis is unknown. These authors showed that increased HGH expression converts mammary carcinoma cells from an epithelial to a mesenchymal phenotype and promotes invasiveness, and that this is caused by decreased expression of γ-catenin.

THERAPEUTICS

An amino-bisphosphonate targets MMP-9 expressing macrophages and angiogenesis to impair cervical cancer.

Giraudo, E., Inoue, M. & Hanahan, D. *J. Clin. Invest.* **114**, 623–632 (2004)

Using a mouse model of cervical cancer, the authors showed that zoledronic acid — a matrix metalloproteinase (MMP) inhibitor used for the treatment of patients with bone metastases — inhibits tumour progression. The drug appeared to function by blocking MMP9, which is involved in activation of vascular endothelial growth factor and induction of angiogenesis.

TECHNOLOGY

Volumetric computed tomography (VCT): a new technology for non-invasive, high resolution monitoring of tumor angiogenesis.

Kiessling, F. *et al. Nature Med.* 7 Sept 2004 (doi:10.1038/nm1096)

Describes a new method to perform high-resolution three-dimensional imaging of tumour-associated blood vessels *in vivo*. The authors analysed the vascular architecture of human carcinoma xenographts with much greater detail than is possible by other available techniques, such as magnetic-resonance angiography, and could clearly distinguish between living and dead tissue. This approach might be useful in monitoring the effect of anti-angiogenic therapies.

LUNG CANCER

Smoking out differences

As if there weren't already enough reasons to give up smoking, a new study has revealed yet another: smokers not only develop lung cancer more often than non-smokers, but differences in the genetic make-up of tumours from the two groups mean that those that arise in smokers are less likely to respond to existing targeted therapies.

Gefitinib selectively inhibits the activity of the epidermal growth factor receptor (EGFR) tyrosine kinase and brings about tumour regression in 10–28% of patients with lung cancer. Pao *et al.* analysed the *EGFR* sequence in tumours from 10 patients with non-small-cell lung cancer (NSCLC) who showed this response, and a further 7 patients who had shown a similar response to a related drug, erlotinib. Of the 17 tumours, 12 (~71%) had mutations in *EGFR*, consistent with the results of previous studies that alterations in this gene are associated with a good response to gefitinib, and indicating that the same holds for erlotinib.

Importantly, 75% of the tumours with *EGFR* mutations were taken from patients classified as 'never smokers' — that is, people who have smoked fewer than 100 cigarettes in their lifetime — and showed an adenocarcinoma histology that is typical of NSCLCs from these patients.

To extend these results, the authors carried out a prospective study of *EGFR* mutations in adenocarcinomas resected from never smokers. They found that 7 out of 15 of these tumours (~47%) carried mutations in the EGFR tyrosine kinase domain. By contrast, for tumours selected at random from current or former smokers, just 5% carried this type of mutation, three-quarters of which were tumours from patients who had given up smoking at least 30 years before surgery. These patterns of *EGFR* mutation indicate that tumours in never smokers are far more likely to respond to gefitinib and erlotinib than those that arise in smokers.

These results provide a molecular basis for previous findings that never smokers show better responses to treatment with gefitinib. However, as only ~10% of lung cancers arise in this group, the most important challenge for the future will be to develop new therapeutic strategies that are effective against the vast majority of lung tumours, which develop in smokers and do not carry *EGFR* mutations.

Louisa Flintoft

References and links

ORIGINAL RESEARCH PAPER Pao, W. *et al.* EGF receptor mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc. Natl Acad. Sci. USA* **101**, 13306–13311 (2004)

WEB SITE

Harold Varmus' lab: http://www.mskcc.org/mskcc/html/10743.cfm