IN THE NEWS

HPV jab success

A vaccine targeting four strains of human papillomavirus (HPV) has reduced infection rates by 90% compared with a placebo in a randomized, double-blind trial, published in *Lancet Oncology*. Eliav Barr, Senior Director of Clinical Research at Merck, who produce the 'Gardasil' vaccine, said it was "… purposefully designed to target the HPV types most commonly associated with cervical cancer, as well as types that cause genital warts and many abnormal Pap smears, to reduce the burden from HPV infection as much as possible." (http://news.bbc.co.uk, 7 April 2005.)

Following the success of the trial, in which 277 women were vaccinated and 275 women were given a placebo, Merck has started a major international trial involving more than 25,000 people. They hope this treatment could be on the market within 2 years. "If Phase III studies demonstrate the vaccine is as effective as [in the smaller trial], I'm sure that it will change the history of cervical cancer," said lead author Luisa Villa, of the Ludwig Institute for Cancer Research, Sao Paulo, Brazil (Reuters, 7 April 2005).

"This vaccine could have a huge impact if you could vaccinate young girls in countries that don't have routine cervical cancer screening," says Debbie Saslow, Director of Breast and Gynaecological Cancer Control for the American Cancer Society. "But these are the countries that are going to be least able to afford it." Nations with comprehensive screening programmes will not replace Pap smears with the vaccine, she suggests, because ~25–30% of cervical cancers are caused by HPV strains that the vaccine does not target (http://www.foxnews.com, 7 April 2005).

Helen Dell

replication forks. Normally, BRCA2 would recruit RAD51 to these sites to carry out HR, but in the absence of functional BRCA2 (and BRCA1, as Ashworth and colleagues show), HR does not occur, prompting the use of error-prone DNA-repair pathways with lethal consequences for the cell.

Helleday and Ashworth also show in their respective papers that the differential sensitivity of *BRCA2*$^{-/-}$ cells to PARP inhibitors is extremely high. So patients who are heterozygous for either BRCA1 or BRCA2 might benefit from a PARP-based treatment strategy, as the tumours arising in these patients are BRCA-null, but the rest of the patients' cells remain heterozygous and therefore unaffected by PARP inhibition. Indeed, the Helleday group suggest that the low toxicity of PARP inhibitors indicates their potential as preventive treatments for BRCA hereditary breast cancer. In addition, as Ashworth and colleagues point out, this work also implies that any tumours with defects within the HR pathway (that is, exhibiting 'BRCAness') might be treatable through inhibiting the function of PARP1.

Nicola McCarthy

References and links

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TUMOUR SUPPRESSORS

Mob-handed?

The Mob superfamily has more than 130 members that are highly conserved through evolution, but their functions are not well understood. Lai and colleagues report a newly discovered family member, MATS (for 'Mob as tumour suppressor'), that has a possible role as a coactivator of protein kinases such as the tumour suppressor WTS.

The authors identified the *mats* gene in fruitflies as a spontaneous lethal muation that increased cell proliferation and caused tumour development in many organs. The *mats*-mutant flies have high levels of key cell-cycle regulators such as cyclins, and show impaired cellular differentiation.

In fly eye discs, *mats* is necessary to downregulate transcription of *diap1*, which encodes a caspase inhibitor that is required for cell survival. Furthermore, introducing the *mats* mutation into flies that already have an apoptosis-promoting defect cancelled out the effects of this defect. This indicates that *mats* facilitates cell death and explains why loss of *mats* might contribute to tumour growth.

Genetic-mapping experiments in the fruitfly identified *mats* as the CG13852 gene, an assignment that was confirmed using CG13852 cDNA to rescue the *mats* mutants. Phylogenetic analysis showed that the *mats* genes form a highly conserved subgroup of the Mob-gene superfamily, with human and plant homologues showing 87% and 64% identity to fly *mats*, respectively. So, MATS protein function is likely to be conserved, and, in fact, the human homologue, *MATS1*, efficiently suppressed the phenotype of *mats*-mutant flies.

Evidence to support the model that MATS might function as a tumour suppressor came from the identification of a destabilizing mutation of *MATS1* in a human melanoma sample, and a null mutation of *Mats1* in a mouse mammary carcinoma.

***mats*-mutant flies have similar phenotypes to flies that are mutant for components of the HPO–SAV–WTS signalling pathway, which regulates cell proliferation and apoptosis, so the authors investigated the relationship between *mats* and *wts*. They found that *mats* and *wts* interact synergistically to control cell proliferation and apoptosis, and that MATS forms a complex with WTS.**

Other Mob-family proteins have been shown to stimulate the catalytic activity of protein kinases. Similarly, MATS markedly stimulated the kinase activity of WTS, and human MATS1 was as effective as fly MATS. WTS also seemed to phosphorylate both itself and MATS/MATS1. Furthermore, inhibiting phosphatase activity notably increased WTS kinase activity, which indicates that phosphorylation of MATS and/or WTS is crucial for WTS function.

So, MATS seems to function as an activating subunit of the WTS kinase in restricting cell proliferation and promoting apoptosis. Moreover, as its effects on growth inhibition and tumour suppression seem to be evolutionarily conserved, MATS might well turn out to be important in human cancers.

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References and links

ORIGINAL RESEARCH PAPER Lai, Z.-C. *et al.* Control of cell proliferation and apoptosis by Mob as tumour suppressor, *Mats. Cell* **120**, 675–685 (2005)

WEB SITE

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