THERAPEUTICS

A positive defect

Patients who lack functional BRCA proteins are at increased risk of developing breast cancer owing to the essential role that these proteins have in DNA repair. Three recent publications in *Nature* have highlighted how BRCA2 functions to regulate DNA repair and how this functional deficit in cancer cells can be exploited therapeutically.

Stephen West and colleagues investigated the interaction between BRCA2 and RAD51. RAD51 is a crucial component of the homologous recombination (HR) repair pathway and interacts with BRCA2 through the BRCA2 BRC-repeat motifs and through an interaction domain in the carboxyl terminus. Current data indicate that this interaction facilitates two essential processes: the formation of RAD51 nucleoprotein filaments, which are essential for RAD51 recombinase activity, and the rapid association of RAD51 with sites of DNA damage. West and colleagues used a series of tagged protein fragments from the C-terminus of BRCA2 to determine the RAD51-interaction motif. They found that phosphorylation of Ser3291 in the C-terminus of BRCA2 regulates the interaction with RAD51. Phosphorylation of this residue is carried out by cyclin-dependent kinases (CDKs) in the G2/M phase of the cell cycle. Furthermore, CDK-dependent phosphorylation was inhibited after DNA damage, facilitating the interaction between RAD51 and the BRCA2 C-terminus and the localization of RAD51 to DNA-damage foci. These findings indicate that BRCA2 Ser3291 phosphorylation regulates the activity of RAD51, preventing its recombinase activity during G2/M but facilitating the repair of any replication-induced strand breaks during S-phase.

Importantly, evidence from human breast cancers indicates that the region around Ser3291 is a mutational hot spot. Loss of the C-terminal portion of BRCA2, but retention of the BRC domains, results in an impaired response to ionizing radiation — RAD51-focus formation is lost and repair of DNA damage through HR is disrupted. Although the isolation of this phosphorylation site might indicate potential strategies for therapeutic intervention, two other papers indicate that tumours that lack BRCA2 (or BRCA1) can be targeted precisely because they cannot carry out HR effectively.

Thomas Helleday and colleagues, and Alan Ashworth and colleagues demonstrate that inhibiting the DNA-repair enzyme poly(ADP)ribose polymerase (PARP) increases the formation of RAD51-repair foci. Previous findings indicate that PARP1 has no direct function in HR, but that the absence of PARP1 increases the need for effective HR repair pathways. The teams both reasoned that spontaneously occurring single-stranded DNA breaks are not repaired effectively in PARP1-deficient cells and that these breaks are likely to be converted into double-stranded DNA breaks during replication, resulting in collapsed ▶

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

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WEB SITE

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