IN THE NEWS

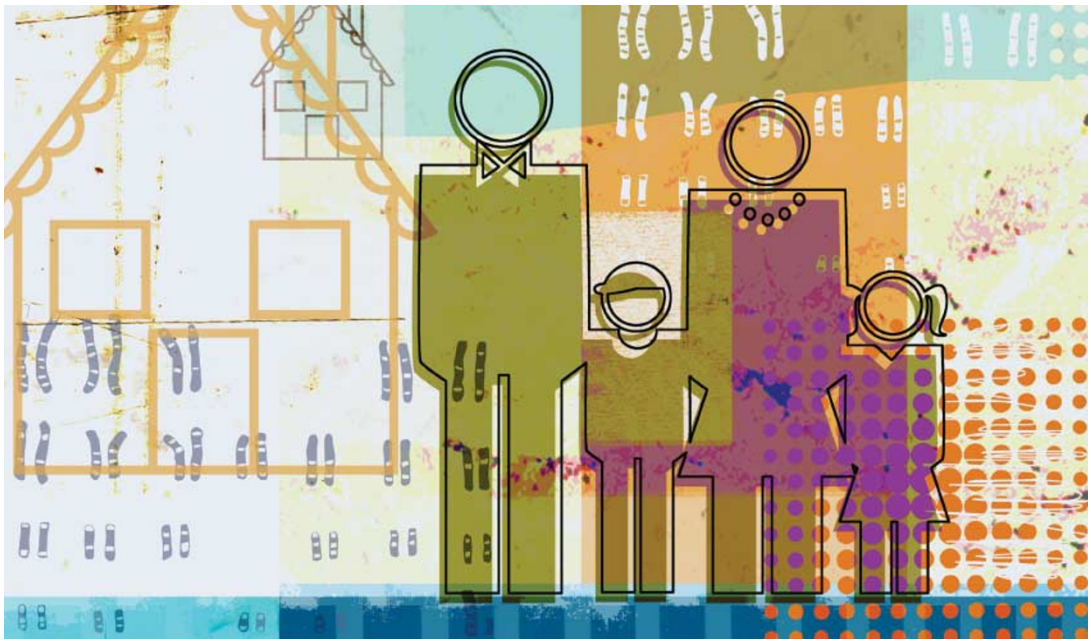
'Mad-cow' mice recover

An astonishing discovery at the Institute of Neurology in London, UK, has revealed that a fatal brain disorder related to mad-cow disease is reversible in mice. Prion diseases — such as bovine spongioform encephalopathy (BSE or mad-cow disease), Creutzfeldt-Jakob disease (CJD) and scrapie — are caused by infection with a misfolded form of normal nerve-cell proteins known as prions. The misfolded prion converts healthy prions into copies of itself and the accumulation of abnormal proteins results in dementia and death.

Giovanna Mallucci and colleagues bred a strain of mutant mice whose nerve cells could be induced to remove normal prions. First, they infected the mice with abnormal prions and allowed the disease to develop. Then the normal prions were depleted and, surprisingly, the disease was halted and early brain damage reversed. According to Mallucci, "It's the conversion process, not the accumulation of protein, that is key to the disease" (*Nature Science Update*, 31 October 2003). "The conversion process might produce a toxic intermediate stage, or it might somehow cause the nerve tissue to break down" (*BBC News Online*, 31 October 2003).

Prion experts are excited by the breakthrough, as previous work — focusing on the abnormal prions — has been disappointing. "We missed the target … it's not the abnormal form but the normal form of the prion protein that has to be attacked", said Jean-Philipe Deslys from the Commission of Atomic Energy, France (*Agence France-Presse*, 30 October 2003). Adriano Aguzzi from University Hospital Zurich, Switzerland, claims, "This is a milestone in prion research" (*Nature Science Update*, 31 October 2003).

Emma Croager



SIGNAL TRANSDUCTION

A new family

Evolutionarily ancient modular BRCT domains are present in many proteins that have roles in the DNA-damage response (cell-cycle checkpoint and DNA repair). However, until now, little was known about exactly how these domains function.

In the first of two papers published in *Science*, Yaffe and colleagues found that two carboxy-terminal tandem BRCT ($(BRCT)_2$) domains of the DNA-damage-response proteins PTIP and BRCA1 bound strongly and specifically to a library of pSer/pThr-Gln phosphopeptides — the phosphorylated motif that is generated by the ATM and ATR kinases that become activated in response to DNA damage. They then determined the optimal binding motifs for these domains, which show strong selection for aromatic and/or alpiphatic residues in the +3 position.

These authors also showed that after DNA damage there was a specific ATM-dependent interaction between PTIP $(BRCT)_2$ domains and the DNA-damage-response protein 53BP1. The $(BRCT)_2$ domains of the amino-terminal PTIP, 53BP1 and MDC1 (a mediator of DNA-damage responses) did not show phosphopeptide discrimination, whereas the budding yeast Rad9 showed only weak phosphopeptide-dependent binding. This led Yaffe and colleagues to conclude that the phosphopeptide-binding function isn't present in all $(BRCT)_2$ domains.

In the second paper, Chen and colleagues focused their attention on the BRCA1 $(BRCT)_2$ domains and their interaction with the putative DEAH-helicase BACH1. Indeed, they found that the BACH1–BRCA1-$(BRCT)_2$ interaction was dependent on the phosphorylation of BACH1 Ser990 and was cell-cycle regulated — BACH1 pSer990 was present only in S-G_2-M cells, as was the BACH1–BRCA1 complex. This interaction was found to be important for activation of the G_2-M checkpoint, which ensures that normal cells damaged by ionizing radiation are arrested and DNA repair is completed before they can enter mitosis (this checkpoint is absent in BRCA1-deficient cells).

Chen and colleagues also found that the intact structure of the $(BRCT)_2$ domains is essential, with the presence of a Phe residue in the +3 position being a major determinant of binding specificity, in agreement with the Yaffe group. In addition, these authors showed that the BRCT domains of Fcp1 and TopBP1 bound to phosphorylated RNA polymerase II and E2F1, respectively, illustrating that the phosphopeptide-specific binding of BRCT domains might be a more general phenomenon.

Reporting in *The Journal of Biological Chemistry*, Songyang and colleagues confirm the BRCA1 $(BCRT)_2$ results of the Chen and Yaffe groups. In contrast to Yaffe and colleagues, they reported that the $(BRCT)_2$ domains of MDC1 did bind specific phosphopeptides. So too did those of BARD1 and DNA ligase IV, although the strength of these interactions seems to be quite weak. The ability of Rad9 $(BRCT)_2$ domains to recognize specific phosphopeptides, albeit weakly, prompted Songyang and colleagues to suggest that this function appeared early in evolution.

So, these three papers begin to unravel the molecular basis for the function of BRCT domains in the DNA-damage response — they provide a link between the kinases that are activated in response to DNA damage and the assembly of multiprotein complexes within the nucleus.

Clearly, there is still much to be learnt; however, as most *BRCA1* mutations result in a truncated protein that lacks one or both BRCT domains and predisposes women to breast and ovarian cancer, the discovery of this new family of phosphopeptide-binding domains has important therapeutic potential.

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References and links

ORIGINAL RESEARCH PAPERS Manke, I. A. *et al*. BRCT repeats as phosphopeptide-binding modules involved in protein targeting. *Science* **302**, 636–639 (2003) | Yu, X. *et al*. The BRCT domain is a phospho-protein binding domain. *Science* **302**, 639–642 (2003) | Rodriguez, M. *et al*. Phosphopeptide binding specificities of BRCT domains. *J. Biol. Chem.* 24 Oct 2003 [epub ahead of print]

WEB SITES

Michael B. Yaffe's laboratory:
http://web.mit.edu/biology/www/facultyareas/facresearch/yaffe.shtml

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