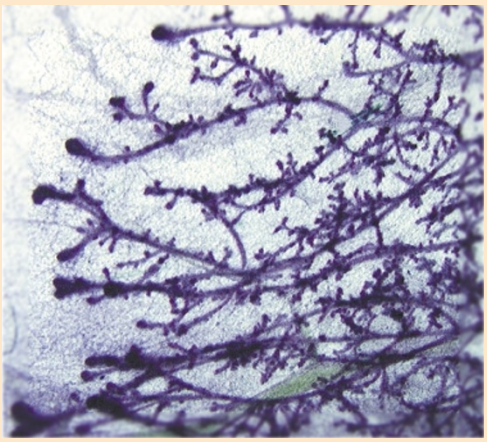
Branching out with BRCA1

While *BRCA1* mutations are known to account for 40–50% of familial breast cancers, an understanding of how they predispose to breast tumorigenesis has been hindered by the lack of a suitable mouse model. Mice heterozygous for a mutation in *Brca1* do not develop tumours, and homozygous embryos die early in development[1–3]. Chu-Xia Deng and colleagues may now have a suitable model; they report, on page 37 of this issue, that mice harbouring a tissue-specific ablation of *Brca1* in mammary epithelial cells develop mammary tumours after a long latency period[4]. According to Barry Gusterson, Professor of Histopathology at the Institute of Cancer Research (who has seen slides of the tumour sections), their histopathology is strikingly similar to that of human breast cancer.

The mutants also display abnormalities in mammary morphogenesis, with smaller glands and ducts that fail to penetrate the fat pad (see figure). How, then, can mutations in *Brca1* activate growth arrest during the development of mammary tissue and yet trigger unrestrained cell proliferation leading to tumorigenesis later in life? An answer to this apparent conundrum may lie in the proposed role of BRCA1 as a 'caretaker', responsible for maintaining genome stability and integrity[5–7]. In the absence of BRCA1, the accumulation of unrepaired damaged DNA is thought to trigger the action of 'gatekeepers', such as p53, leading to a growth arrest response—and this may account for the increased apoptosis observed in the mammary glands of the conditional *Brca1* mutant mice. Loss of BRCA1 may set the stage for gradual genome stability 'melt down', with mutations manifesting in a multitude of genes, including *TP53* (which encodes p53). BRCA1-deficient cells that acquire subsequent mutations in *TP53* are anticipated to overcome p53-mediated cell-cyle arrest and undergo unrestrained cell proliferation leading to tumorigenesis. Indeed, Deng and colleagues find that many mammary tumours in the conditional mutant mice harbour gross chromosomal rearrangements, including disruption of *Trp53*, the mouse homologue of *TP53*. This is consistent with reports that *TP53* mutations are common in human *BRCA1* familial breast cancer[8,9].



Branching endbuds of the mammary ducts fail to penetrate the fat pad in *Brca1* conditional mutant mice.

To test whether inactivation of *Trp53* contributes to progression of *Brca1*-associated tumorigenesis, Deng and colleagues introduced a *Trp53*-null allele into the conditional *Brca1* mutant mice and found that tumour formation was accelerated. The majority of tumours had lost the remaining wild-type *Trp53* allele, suggesting that inactivation of *Brca1* may drive the loss of *Trp53*. It is likely, however, that the genomic instability arising from *Brca1* loss leads to inactivation of several tumour suppressors, which may account for the diverse tumour morphology seen in *Brca1* conditional mutant mice and human *BRCA1* breast cancer patients.

The conditional mutant mice offer a model to study molecular aberrations arising from *Brca1* deficiency, identify genetic modifiers and exogenous factors that influence the onset of tumour formation, and validate potential therapeutic strategies. An indication of how accurately tumour progression in these mice mimics that of human breast cancer patients awaits assessment of whether the tumours are invasive, demonstrate lymph node spread and metastasize to brain, bone, liver and lung—the sites commonly infiltrated in the human disease.

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