What do we know about how the wild-type *APC* allele is lost? Elegant studies by Haigis and Dove suggest that it is usually lost in the adenomas of $APC^{Min/+}$ heterozygous mice by somatic recombination[11]. Partial chromosomal allelic imbalance produced by somatic recombination might seem inconsistent with the whole chromosomal allelic imbalance that is expected from the resolution of a tetraploid intermediate. However, the rate of gene conversion (nonreciprocal gene transfer that can be driven by recombination) is high in yeast tetraploids, raising the possibility that products of reduction mitoses may evince an increased frequency of somatic recombination[12].

Is the lack of spindle-cortical interactions the root cause of cytokinetic failure, or are there other underlying defects in *APC*-mutant cells? An earlier study by Dikovskaya *et al.*[6] likewise found that *APC*-mutant cells did not undergo cytokinesis, but these authors ascribed this failure to an attenuated spindle checkpoint and to 'mitotic slippage'. Mitotic slippage describes the escape of cells from a prolonged spindle checkpoint arrest without segregation of chromosomes, thus leading to the generation of tetraploid cells[13]. Dikovskaya *et al.*[6] inhibited APC function with RNAi, and the results may be indicative of an *APC*-null phenotype.

The differences in mechanism suggest that defective APC function can lead to tetraploidy in two ways: dominant truncation mutations may abrogate spindle-cortical interactions, and complete loss of APC function may result in mitotic slippage (**Fig. 1**). The mechanism of cytokinetic failure may also depend on the tissue type or genotype of the cells used. Nevertheless, these two studies together highlight the many ways of generating tetraploid cells that may serve as intermediates in tumor formation.

How prevalent are tetraploids in *APC*-mutant tissues? Caldwell *et al.*[5] estimate that roughly 5% of normal and dysplastic intestinal epithelial cells in $APC^{Min/+}$ mice are tetraploid. The chromosomal complement of adenomas in these mice was previously examined and found to be no different than that of matched normal tissue[14]. Although the previous data may indicate that adenomas contain no tetraploid cells, these data must be carefully interpreted in light of the Caldwell *et al.*[5] study. As shown by Caldwell *et al.*[5], histologically normal tissues in $APC^{Min/+}$ mice appear to sustain a low level of tetraploidy without pathologic progression. Because tetraploids are present in normal tissue, a comparison between adenomas and normal tissue would not uncover these tetraploid cells. However, adenomas truly may not have tetraploids, whereas the dysplasias and normal tissue studied by Caldwell *et al.*[5] do. The absence of tetraploids in adenomas would be possible if the rate of resolving tetraploid cells into diploid cells, compared to the rate of making tetraploid cells, is much higher in adenomas than it is in hyperplasias.

Although it is intriguing that *APC* mutation can induce tetraploidy *in vivo*, it still remains to be shown that it is the tetraploid cells that give rise to tumors. However, there is increasing evidence that tetraploid cells are relevant in some cancers. They are present in premalignant tissues such as Barrett's esophagus and melanocytic nevi, as well as in plasma cell leukemias and in cervical and other cancers. Importantly, tetraploidy has been shown to promote breast-tumor formation in mice[15].

For most cell types examined, tetraploidy confers a growth disadvantage. However, the genomic instability associated with tetraploids can yield a vast array of daughter cell genotypes, some of which may confer beneficial growth and survival properties to an aspiring cancer cell.

1. Shih, I.M. *et al. Cancer Res.* **61**, 818–822 (2001).
2. Wood, L.D. *et al. Science* advance online publication, 11 October 2007 (doi:10.1126/science.1145720).
3. Martin, G.M. & Sprague, C.A. *Exp. Cell Res.* **63**, 466–467 (1970).
4. Wang, X. *et al. Nature* **422**, 897–901 (2003).
5. Caldwell, C.M. *et al. J. Cell Biol.* **178**, 1109–1120 (2007).
6. Dikovskaya, D. *et al. J. Cell Biol.* **176**, 183–195 (2007).
7. Kinzler, K.W. & Vogelstein, B. *Cell* **87**, 159–170 (1996).
8. Segditsas, S. & Tomlinson, I. *Oncogene* **25**, 7531–7537 (2006).
9. Näthke, I. *Nat. Rev. Cancer* **6**, 967–974 (2006).
10. Spirio, L. *et al. Cell* **75**, 951–957 (1993).
11. Haigis, K.M. & Dove, W.F. *Nat. Genet.* **33**, 33–39 (2003).
12. Storchova, Z. *et al. Nature* **443**, 541–547 (2006).
13. Rieder, C.L. & Maiato, H. *Dev. Cell* **7**, 637–651 (2004).
14. Haigis, K.M. *et al. Proc. Natl. Acad. Sci. USA* **99**, 8927–8931 (2002).
15. Fujiwara, T. *et al. Nature* **437**, 1043–1047 (2005).

Seeking the source of schizophrenia

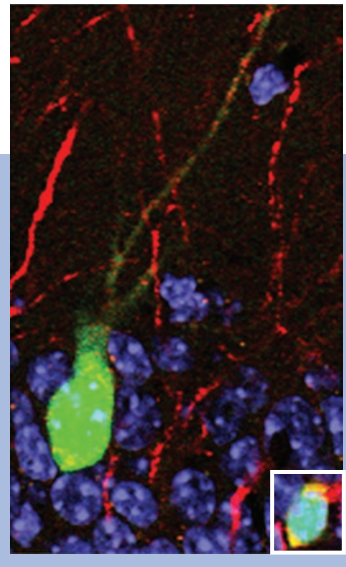
Aberrant neurogenesis in the adult brain may have a role in schizophrenia, hints a study in mice (*Cell* **130**, 1146–1158).

Xin Duan *et al.* examined the function of disrupted in schizophrenia-1 (DISC1) a schizophrenia susceptibility gene expressed in regions of the adult brain that undergo continuous neurogenesis, including the hippocampus. The researchers knocked down the gene with small hairpin RNAs targeted to DISC1.

DISC1 knockdown resulted in accelerated morphological development of adult-born neurons, including the enlargement of neuronal cell bodies, as shown here. Additional defects included mispositioning of new neurons, more mature neuronal firing patterns, and accelerated dendritic development and synapse formation. The researchers conclude that DISC1 helps control the timing of neuronal integration in the adult brain.

DISC1 also operates during embryonic development, which is consistent with the view that schizophrenia originates during early brain formation. But whether the embryonic or the adult activity of the gene holds sway in the development of disease remains to be seen.

—Charlotte Schubert



Neurons lacking DISC1 sport abnormally large cell bodies. DNA in blue, immature neurons in red and cells expressing shRNAs to DISC1 in green; inset shows size of neuron with intact DISC1 expression.