zle was fitted into place with the discovery of a family of nuclear transcription factors that bind β-catenin/armadillo. Upon Wnt signaling, free cytoplasmic β-catenin associates with Tcf, a member of the high-mobility-group (HMG) box transcription factor genes, and presumably promotes transcription of target genes[17]. This hypothesis was recently confirmed in flies, where an armadillo-Tcf complex was found to act as a bipartite transcription factor in mediating wingless signaling[18].

How does Wnt-β-catenin signaling relate to colorectal cancer? Adenomatous polyposis coli (APC), a condition predisposing to colon cancer, is initiated by mutations in the APC gene. Taking into account the two interactions: β-catenin with APC and β-catenin with transcriptional elements, researchers in the field hypothesized that APC might regulate the formation of the β-catenin-Tcf transcription complex. Groups led by Clevers and Kinzler have now shown that transcription by β-catenin–Tcf is altered in cells harbouring APC mutations[1,2]. As predicted by the fact that APC mediates β-catenin degradation, loss of APC function in APC–/– carcinoma cells resulted in uncontrolled transcriptional activation of β-catenin–Tcf-4 target genes. These findings suggest that APC-mediated down-regulation of free-β-catenin suppresses colorectal tumorigenesis. However, if this is the case, how do we explain colorectal cancers in patients with wild-type (WT) APC? On investigating two cell lines from such cancers, Morin *et al.* found that both carry missense mutations in the β-catenin gene itself[2]. Perhaps not surprisingly, both mutations affected serine residues previously implicated in the down-regulation of β-catenin by GSK-3β kinase in Xenopus embryos[15], further supporting the idea that accumulation of cytoplasmic β-catenin might play a central role in the onset of colorectal malignant transformation.

Additional pieces in the β-catenin signaling puzzle will be supplied on the identification of the β-catenin/Tcf-4 responsive genes and their roles in colon cancer transformation. In the meantime, efforts continue to unravel the various means by which adhesive function and signaling activity are related and coordinated in the same cell. The current evidence suggests that adhesive and signaling interactions are intertwined; given the numerous, sophisticated responses of the cell to environmental stimuli, further links between the disparate worlds of signaling and adhesion should come as no surprise. □

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Inside out, boy you turn me?

Genome fluidity is limited by several factors, two of which are sequence constraints and the viability of the prescribed phenotype. On page 96, Kersten Small and colleagues present data that reflect both; their dissection of a deletion on the X chromosome in Emery-Dreifuss muscular dystrophy (EMD) encompassing the emerin gene, suggests models that twist chromosomes (and the imagination) into alternative configurations[1].

Intra- and inter-chromosomal misalignment of long repeats — motifs of nearly-identical sequence that occur in *cis* and sandwich intervening sequence — have been implicated as the cause of several disorders. Intrachromatid recombination via the parallel alignment of two inverted repeats is known to disrupt factor VIII, giving rise to haemophilia A[2], and has been recently indicted as a cause of Hunter syndrome[3]. Large repeats also bear the burden of blame in Charcot-Marie-Tooth syndrome[4], although here, interchromosomal misalignment is proposed, whereby a repeat proximal to the critical *PMP-22* gene misaligns with a distal repeat and recombination between the two clinches a duplication. In this case, however, the repeats are necessarily in the same direction.

The X-chromosomal rearrangement revealed by Small *et al.* implies a combination of these features: the long, highly homologous repeats that flank the critical region in EMD are inverted, but the shuffled contents of the intervening region in a patient with EMD suggest a more exotic mechanism involving interchromosomal alignment (see Fig. 1). On recognising the potential of these impressive repeats (each is approximately 11.3 kb and has 99% sequence identity with the other), Warren and colleagues examined normal X chromosomes and, surprisingly, found that 33% of females carry an inversion between them. How does this happen? Is the inversion intrachromosomally mediated, with a single recombination event, or interchromosomally mediated, with recombination occuring in both repeats?

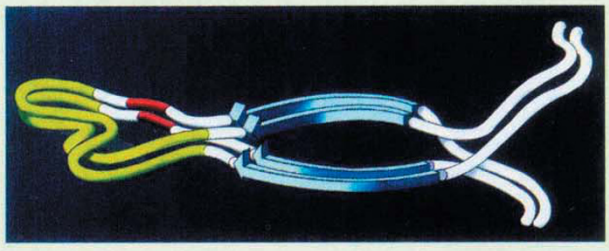

Fig. 1 Model: long inverted repeats may facilitate interchromosomal 'misalignment', with double recombination generating inversions and other rearrangements.

Assigning maternal or paternal inheritance to these inversions may help to answer this question — a study of the exchange leading to haemophilia A suggests that intrachromatid exchange is roughly 300 times more common in male than in female gametogenesis[5]. While the sex effect on the 'emerin' inversion has yet to be assessed, the current study provides a neat resolution of the discrepancy between physical mapping and the low recombination frequency noted in this region, and an instructive lesson for those faced with such discrepancies in other areas of the genome.

— Bette Phimister

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