STRUCTURE WATCH

There are rings…

The DNA polymerase III holoenzyme, which carries out chromosomal DNA replication in *Escherichia coli*, comprises three main parts: the catalytic core, responsible for DNA synthesis; the doughnut-shaped sliding clamp (a head-to-tail dimer of β-subunits), which confers processivity; and the clamp-loading (or γ) complex, that consists principally of the γ-, δ- and δ'-subunits. The clamp-loading complex binds to and opens the β-clamp, which allows it to encircle the duplex DNA, and these authors have investigated how it does this by solving the crystal structures of a complex between the δ-subunit and the β-ring, and also of the entire γ-complex.

The authors propose that the mechanism by which the β–δ interaction leads to opening of the β-ring involves two components: first, the δ subunit acts as wrench, preventing the β-ring from closing; and second, the ring-opening mechanism is 'spring loaded' (the curvature of the β-monomer in the β–δ complex is reduced relative to within the β-dimer), supplementing the action of the δ-wrench.

The structure of the γ-complex uncovers a further twist. The subunits are arranged as a pentamer, with the stoichiometry $\delta':\gamma_3:\delta$. This asymmetric arrangement, say the authors, might support a mechanism in which the γ-complex switches between two forms — a 'closed' state, in which the δ-subunit is prevented from interacting with the β-clamp by δ'; and an 'open' state, in which δ is free to engage the β-ring.

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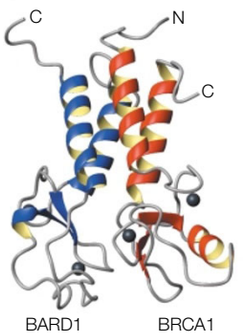
…and RINGS

Twenty per cent of clinically relevant mutations in the BRCA1 tumour suppressor occur within the amino terminus. This region harbours a RING domain, through which BRCA1 interacts with other proteins, including BARD1. Brzovic *et al.* now report the solution structure of the heterodimer between the BRCA1–BARD1 RING domains (pictured). A comparison of this RING–RING interaction with that seen between two RAG1 homodimers shows the structural diversity of the interactions between different RING domains.

At the carboxyl terminus of BRCA1 is found the BRCT region, which is essential for the function of the protein in DNA repair and transcription. Williams *et al.* have solved the crystal structure of this region and mapped mutations that predispose to cancer onto the structure. They show that the BRCT domain contains two BRCT repeats that are arranged in a head-to-tail fashion. Mutations occur at the interface of these repeats, hence destabilizing the structure.



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CYTOSKELETON

Making the cap fit

The actin cytoskeleton has crucial roles in cell and tissue morphogenesis, in which it orders cellular space and transduces forces. New work in the October issue of *Nature Cell Biology* by Baum and Perrimon identifies the genes that control the polarized distribution of actin filaments in the *Drosophila* follicular epithelium.

Actin filaments are involved in processes as wide-ranging and diverse as cytokinesis, polarized intracellular transport, adhesion and migration. Therefore, the action of F-actin must be regulated in both a temporal and spatial manner to ensure 'the cap always fits' — in other words, to tailor the level and localization of actin to the required biological function. Many studies have identified the proteins that are needed for actin polymerization and depolymerization; for example, Enable (Ena) and VASP catalyse actin formation, whereas adenylyl-cyclase-associated proteins (CAP proteins) limit polymerization. However, little is known about the function of actin-regulatory proteins within an intact organism.

Baum and Perrimon used both genetics and cell biology in *Drosophila melanogaster* to study the spatial control of actin within the follicular epithelium. The follicle cells surround the germ-line cyst and, during oogenesis, undergo at least two significant shape changes. So, they are an ideal system in which to study the regulation of actin dynamics. By generating clones of cells that lack Ena, CAP (a *Drosophila* CAP protein homologue) or Abelson (Abl, a tyrosine kinase, which acts as a CAP-binding protein), Baum and Perrimon were able to study the role of each of these genes in modulating the spatial organization of the actin cytoskeleton within these cells. Clones of follicle cells which lack CAP maintain their epithelial polarity, but have increased levels of actin and defects in actin organization. (In the figure, CAP clones within the follicle cell epithelium, which are marked by the absence of green fluorescent protein (green), have increased levels of actin (pink) and Ena (blue) at the apical membrane.) Similarly, Abl clones also have subtle defects in actin

B-CELL BIOLOGY

Keeping alleles quiet

With rare exceptions, each lymphocyte is destined to express only one antigen-receptor specificity for life, but the mechanisms by which this is enforced have not been fully resolved. During B-cell development, immunoglobulin gene segments — variable (*V*), diversity (*D*) and joining (*J*) — recombine to form functional immunoglobulin genes, generating a diverse B-cell repertoire. Regulated expression of the recombination activating genes (*RAG1* and *RAG2*) during B-cell development helps to ensure that each B cell expresses a single heavy (IgH) chain and a single light-chain (Igκ or Igλ) allele, a phenomenon known as allelic exclusion. Now, reporting in *Nature Immunology*, Skok *et al.* provide the first evidence that epigenetic mechanisms could reinforce monoallelic expression of immunoglobulin genes at later stages.

Previous studies have shown that many inactive genes localize to centromeric heterochromatin in the nucleus of actively dividing lymphocytes, in association with Ikaros (a DNA binding protein that is essential for B and T cell development). This led to the proposal that the recruitment of loci to heterochromatic domains might lead to heritable silencing of genes. In the current study, the three-dimensional nuclear