Putting condensin in its place

A new study provides a genome-wide map of binding sites for condensin, a protein complex essential for chromosome condensation and sister chromatid resolution (*Genes Dev.* **22,** 2215–2227; 2008). By analysing condensin chromatin immunoprecipitates on oligonucleotide tiling arrays, D'Ambrosio *et al.*, derived a minimal condensin binding site. Binding is enriched at tRNA genes and other pol III target genes in budding and fission yeast. Condensin colocalizes with the pol III transcription factor TFIIIC on the B-box promoter element of pol IIII genes. Indeed, the B box represents a minimal condensin binding motif. Maximal binding, however, is also likely to require other sequence elements. This analysis demonstrates that Scc2/4, which loads the cohesin complex that acts in chromosome segregation, is also important for condensin binding and thus for chromosome condensation. Furthermore, TFIIIC recruits and/or stabilizes Scc2/4 and condensin on chromosomes. Understanding how condensin binds will no doubt provide fresh insights into its function in chromosome biology. SS

Wnt pathway selection

Wnt proteins control a variety of developmental processes through independent signalling cascades. The canonical Wnt pathway leads to stabilization of β-catenin, whereas another pathway increases intracellular Ca^{2+} and a third regulates planar cell polarity (PCP). Specification of Wnt signalling is partly achieved by binding of Wnt ligands to distinct receptors and co-receptors but other mechanisms are likely to be involved. Yamamoto and colleagues (*Dev. Cell* **15,** 23–36; 2008) now show that the secreted protein Cthrc1 (collagen triple helix repeat containing 1) exclusively mediates the activation of the PCP pathway by Wnt. The authors identified Cthrc1 in a screen for genes expressed in the embryonic node and notochord. Later in development Cthrc1 was also present in other tissues and its expression pattern overlapped with that of the PCP receptor Fzd6. *Cthrc1* null mice are phenotypically normal, but crossing with mice heterozygous for the PCP gene *Vangl2* results in a PCP mutant phenotype similar to that of the *Vangl2* null, demonstrating genetic interaction of *Cthrc1* and *Vangl2*. Cthrc1 anchored to the cell surface binds both canonical and non-canonical Wnt signalling components; however, it selectively activates the Wnt/PCP cascade by enhancing the interaction between Wnt, Fzd receptors and the Wnt/PCP co-receptor Ror2. These findings suggest that other factors restricting Wnt signalling will emerge. CK

Kick-starting anaphase

In mitotic anaphase, chromosome pairs are pulled apart on loss of sister-chromatid cohesion. Cohesion is rapidly and irreversibly disrupted following degradation of securin by the ubiquitin ligase anaphase-promoting complex (APC). This activates the protease separase, which targets cohesin. In search of regulatory mechanisms enabling such switch-like behaviour in budding yeast, Morgan and colleagues have uncovered a positive-feedback loop that increases the abruptness of anaphase through modulation of securin ubiquitylation (*Nature* **454,** 353–357; 2008). Cdk1-dependent phosphorylation of a previously uncharacterized site near the destruction-box of securin inhibited its ubiquitylation by APC. Conversely, dephosphorylation by Cdc14 increased securin ubiquitylation. As separase activates Cdc14 in early anaphase, a positive-feedback model is proposed: when APC activity peaks, securin is partially destroyed, activating separase; this triggers anaphase through Cdc14-dependent dephosphorylation of securin, facilitating its degradation by APC. Modulation of securin by Cdk1 and Cdc14 is required for an abrupt anaphase and for coordinated spindle dynamics, as disruption of securin phosphorylation altered the timing and processivity of chromosome segregation. This feedback mechanism ensures that the cell is irreversibly committed to sister-chromatid separation once initiated. SG

Unshackling Ku from DNA

The heterodimer Ku70/Ku80 is the core component of non-homologous end joining (NHEJ), a key repair pathway for double-stranded DNA breaks (DSBs) and VDJ recombination. It was unclear how the Ku70/Ku80 ring is removed from DNA after repair. Funabiki and colleagues now report that Ku80 is removed by ubiquitylation and degradation in response to DSBs (*J. Cell Biol.* doi: 10/1083/jcb.200802146; 2008). A DSB binding assay in *Xenopus* extracts identified several known DSB-associated proteins along with Ku-dependent binding of the ubiquitin ligase SCF. Many of these proteins were polyubiquitylated through Lys 48 linkages independently of the kinases ATM and ATR. Dominant-negative ubiquitin mutants and proteasome inhibitors confirm that Ku80 is subject to DSB-induced Lys 48 polyubiquitylation and proteasomal degradation. Interestingly, the release of Ku80 from DNA is dependent on ubiquitylation, but not degradation. NEHJ repair is not required for Ku80 ubiquitylation or degradation. Conversely, Ku80 removal is not required for NHEJ. Although SCF is a good candidate for mediating Ku80 ubiquitylation, the ubiquitin ligase and ubiquitylation sites remain to be identified. However, the authors show that the DNA binding region of Ku80 is sufficient for ubiquitylation and degradation. The mechanism of how polyubiquitylation induces the Ku70/Ku80 ring to release its grip on DNA will undoubtedly emerge soon. BP

MicroRNAs go large on protein synthesis

MicroRNAs (miRNAs) control protein levels by inhibiting translation and/or inducing degradation of mRNA. So far there has been no large-scale analysis of the relative importance of these two mechanisms. Selbach *et al.* (doi:10.1038/nature07228) and Baek *et al.* (10.1038/nature07242) measured global changes in protein and mRNA levels after ectopic expression or silencing of a handful of miRNAs. Both groups found that a given miRNA can regulate translation of hundreds of proteins, although most mRNA targets are repressed only weakly. Cell proteomes were assessed using stable isotope labelling with amino acids in cell culture followed by mass spectrometry. mRNA levels were measured in parallel by microarray. Bioinformatic analysis confirmed that a 7–8mer matching the miRNA binding sequence in the 3´UTRs of target mRNAs strongly correlates with repression. Baek *et al.* showed that only one miRNA binding site can mediate inhibition. Although miRNAs can act exclusively at the translation level, the targets repressed most also showed the greatest changes in mRNA, highlighting that effective repression probably requires degradation of mRNA targets. Selbach *et al.* showed that *let-7* miRNA expression correlated with downregulation of *DICER* miRNA translation, which encodes an enzyme involved in miRNA production, suggesting that *let-7* also acts indirectly on many other targets. Thus a given miRNA subtly adjusts a large fraction of the proteome. NLB

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