MEIOTIC RECOMBINATION

Controlled crossing-over

At meiosis, recombination — or genetic crossing-over — is initiated by the formation of DNA double-strand breaks (DSBs). But, how breakage of the chromosomes is controlled has been a mystery. Even though the influence of chromatin has long been suspected, only recently have several studies, including one by Reddy and Villeneuve in *Cell*, indicated a possible role for histone modifications in DSB formation.

Reddy and Villeneuve identified the *Caenorhabditis elegans him-17* gene in a genetic screen and found that *him-17* mutants were defective in meiotic segregation of homologous chromosomes. The mutants also lacked chiasmata (the cytologically visible connections between homologous chromosomes that correspond to the position of the crossover), which reflects a failure to form crossovers. However, immunofluorescence studies showed that *him-17* mutants did form normal pairs of homologous chromosomes, which were connected by a synaptonemal complex (the protein structure that holds the paired chromosomes together). So, the lack of crossover formation was not due to a defect in homologous pairing, or synapsis, but was probably caused by a defect in the recombination process itself.

An antibody against the DNA-strand-exchange protein RAD-51 — which associates with recombination intermediates — showed reduced staining in the nuclei of *him-17* mutants compared with wild-type germlines. In addition, the induction of DSBs by γ-irradiation in *him-17* mutants rescued the mutant phenotype, as efficient chiasmata formation occurred. This result was reminiscent of the rescue by artificially induced DSBs of the mutant phenotype of the topoisomerase-like protein SPO-11, which is necessary for initiating meiotic recombination through DSB formation. These and other data strongly imply that HIM-17 is required for DSB formation.

Using worms that carried a HIM-17 fluorescent fusion protein, the authors showed that HIM-17 localizes mainly to chromatin in germline nuclei during all meiotic stages up until diakinesis when the chromosomes are well separated. Given that HIM-17 seems to be associated with chromatin, Reddy and Villeneuve stained germlines with antibodies against specific histone modifications, and looked for differences between wild-type and *him-17*-mutant germlines. Interestingly, staining with an antibody against histone-H3 dimethyl-lysine 9 (H3MeK9) — a histone modification that is typical of compact, or 'closed', heterochromatin — showed reduced and/or delayed accumulation in the mutant.

The authors identified structural features that were shared between HIM-17 and three proteins that interact genetically with *lin-35/Rb* — which has been implicated in chromatin-modifying complexes. The loss of LIN-35/Rb enhanced the meiotic defects of *him-17* partial loss-of-function mutants, which indicated that LIN-35/Rb itself can modulate DSB levels.

Reddy and Villeneuve propose that the HIM-17-dependent progressive compaction of the chromatin during meiotic prophase establishes "competence for DSB formation". Several recent studies in yeast have also implicated histone modifications in DSB formation. However, whether there is a direct molecular link between histone modification and DSB formation remains to be established.

Arianne Heinrichs

References and links

ORIGINAL RESEARCH PAPER Reddy, K. C. & Villeneuve, A. M. *C. elegans* HIM-17 links chromatin modification and competence for initiation of meiotic recombination. *Cell* **118**, 439–452 (2004)

STRUCTURE WATCH

An endosomal escort

Transmembrane proteins and lipids are delivered to the endosomal lumen by the multivesicular-body sorting pathway — a pathway that is important for receptor downregulation and viral budding. The sorting process requires a ubiquitin signal and the transfer of ubiquitylated cargo between the protein complexes ESCRT-I, -II and -III (endosomal sorting complexes required for transport). And now, in *Nature*, Hurley and colleagues provide valuable insights into this process by describing the 3.6-Å-resolution crystal structure of the core of yeast ESCRT-II.

ESCRT-II is composed of Vps22 (vacuolar protein sorting-22), Vps36 and two molecules of Vps25, and the core structure is a rigid 'Y' shape. One molecule of Vps25 forms the base of the Y, the second forms a branch, and a Vps22–Vps36 subcomplex (which contains only the carboxy-terminal region of Vps36 owing to proteolysis) makes up the second branch. The amino-terminal coiled coil of Vps22, which has been predicted to interact with coiled coils in ESCRT-III subunits, protrudes from the tip of the second branch, as does the flexible linker of Vps36 that leads to its ubiquitin-binding domains. Hurley and co-workers therefore propose that larger oligomers of the three ESCRT complexes might form an ordered scaffold, which prevents ubiquitylated cargo diffusing away from the low-affinity binding sites in these complexes. In addition, they propose that the complexes have "…long swinging arms for the transfer of cargo over distances of tens to hundreds of Å". This structure-based conceptual framework takes us a step closer to a complete mechanistic understanding of this pathway.

REFERENCE Hierro, A. *et al.* Structure of the ESCRT-II endosomal trafficking complex. *Nature* **431**, 221–225 (2004)

Protected from birth

As they emerge from a ribosomal exit tunnel, newly synthesized proteins are met by chaperones that help them fold into their native state, and the principle of ribosome-associated chaperones has been conserved in prokaryotes and eukaryotes. But how do such chaperones support protein folding? Ban and colleagues now shed light on the matter in *Nature*.

They describe the 2.7-Å-resolution crystal structure of the most well-characterized ribosome-associated chaperone, trigger factor (TF) from *Escherichia coli*. In addition, they describe the 3.5-Å-resolution crystal structure of an amino-terminal TF fragment that is bound to the large ribosomal subunit of *Haloarcula marismortui*. They found that TF adopts a "crouching dragon" shape. The amino-terminal, ribosome-binding domain forms the tail, the carboxy-terminal domain makes up the arms and the back and, together, these domains form an arch. The peptidyl-prolyl isomerase domain, which is not essential for the chaperone activity of TF, forms the head. By combining their structural data, the authors show that TF seems to hunch over the ribosomal exit tunnel, extending the hydrophobic inner face of the arch towards the nascent polypeptide and providing a well-defined, shielded 'cage' for protein folding. This cage can hold a folded protein domain, and these data have highlighted "…an unexpected mechanism of action for ribosome-associated chaperones".

REFERENCE Ferbitz, L. *et al.* Trigger factor in complex with the ribosome forms a molecular cradle for nascent proteins. *Nature* 29 Aug 2004 (doi:10.1038/nature02899)