Condensin and cohesin complexity: the expanding repertoire of functions

Andrew J. Wood[*‡§], *Aaron F. Severson*[*§] *and Barbara J. Meyer*[*]

Abstract | Condensin and cohesin complexes act in diverse nuclear processes in addition to their widely known roles in chromosome compaction and sister chromatid cohesion. Recent work has elucidated the contribution of condensin and cohesin to interphase genome organization, control of gene expression, metazoan development and meiosis. Despite these wide-ranging functions, several themes have come to light: both complexes establish higher-order chromosome structure by inhibiting or promoting interactions between distant genomic regions, both complexes influence the chromosomal association of other proteins, and both complexes achieve functional specialization by swapping homologous subunits. Emerging data are expanding the range of processes in which condensin and cohesin are known to participate and are enhancing our knowledge of how chromosome architecture is regulated to influence numerous cellular functions.

Catenations
Topological linkages between duplex DNA. Catenations between sister chromatids arise during replication.

*Howard Hughes Medical Institute and Department of Molecular and Cell Biology, University of California-Berkeley, 16 Barker Hall, MC 3204, Berkeley, California 94720-3204, USA.
‡Department of Medical and Molecular Genetics, King's College London, Guy's Hospital, London SE1 9RT, UK.
§These authors contributed equally to this work.
Correspondence to B.J.M.
e-mail: bjmeyer@berkeley.edu
doi:10.1038/nrg2794
Published online 5 May 2010

Chromosomes undergo essential changes in morphology that promote proper expression and maintenance of the genome. These changes are mediated, in part, by structural maintenance of chromosomes (SMC) proteins that restructure the genome by promoting interactions between some chromosomal sites while inhibiting others. SMC proteins form the core of multiprotein complexes that use energy from ATP hydrolysis to organize chromosomes in the nucleus. Two SMC complexes, condensin and cohesin (BOX 1), were initially identified through their roles in chromosome restructuring during mitosis, but they are now known to have additional nuclear functions. In this Review, we focus on four such areas in which the involvement of condensin and cohesin has received much recent attention: organization of the interphase genome, regulation of gene expression, metazoan development and meiosis. We then consider where and how these complexes are loaded onto chromosomes and how functional diversity is achieved.

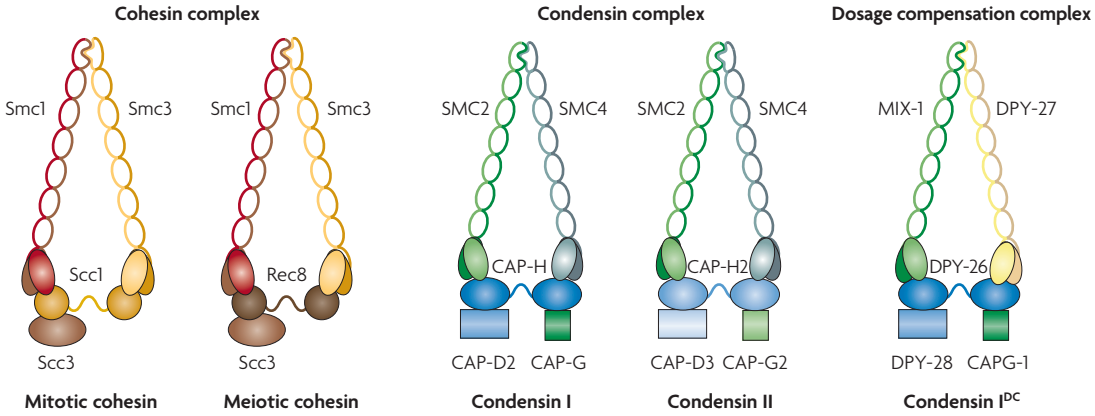
Condensin and cohesin are both major components of mitotic chromosomes. Cohesin generates sister chromatid cohesion (SCC), which holds sister chromatids together from S phase until mitosis, when cohesion is removed to allow chromosome segregation (BOX 2). Condensin is important during mitosis for the timely compaction and resolution of chromosomes to remove and prevent catenations that would otherwise inhibit segregation (BOX 2). A third complex, SMC5–SMC6, participates in DNA repair and shares compositional features with condensin and cohesin[1] but is not discussed in this Review. The mitotic roles of condensin and cohesin, together with important insights into the molecular mechanisms of condensin and cohesin function, have been reviewed elsewhere[2–4] and are therefore not extensively described here.

Whether common molecular mechanisms underlie all of the diverse biological processes in which condensin and cohesin act is not presently known. However, unifying principles are emerging from the work described here regarding the way in which the complexes function and can become specialized. In light of the range of biological processes in which condensin and cohesin function, it is our hope that this Review will be useful to scientists working in all aspects of nuclear biology and genetics.

SMC complexes in genome organization

Interphase processes such as transcription and DNA repair depend on dynamic interactions between distant DNA elements. The interphase genome is partitioned into independently regulated domains that are thought to consist of loops of DNA stabilized by chromosomal proteins (BOX 3). SMC complexes participate in demarcating domain boundaries along the one-dimensional DNA fibre and in organizing these domains in three-dimensional space in the nucleus. In the following section, we review the evidence implicating

Box 1 | **Anatomy of SMC complexes**



Condensin and cohesin complexes are conserved from bacteria to humans. Members of both complexes contain a pair of structural maintenance of chromosomes (SMC) subunits and ancillary non-SMC subunits. All SMC proteins share five domains[4]. At the amino and carboxyl termini lie two nucleotide-binding domains (NBDs) called the Walker A motif and the Walker B motif, respectively. The NBDs are linked by two long (40–50 nm) coiled coils separated by a 'hinge' domain. Each SMC protein folds back on itself to form a central region composed of the two antiparallel coiled coils flanked on one end by the hinge domain and on the other end by a head domain composed of the two NBDs. The two SMC proteins dimerize through interactions between their hinge domains and bind the non-SMC subunits through interactions with the head domains. Most known SMC heterodimers associate with a non-SMC subunit of the 'kleisin' family; the subunit interacts with the two head domains and thereby forms a closed ring. Because of this geometry, it has been proposed that SMC complexes perform their functions by encircling one or more DNA strands.

Cohesin

Mitotic cohesin complexes contain a heterodimer of Smc1 and Smc3, the non-SMC subunit sister chromatid cohesion 3 (Scc3), and the α-kleisin subunit Scc1. In most organisms, meiotic cohesin complexes contain the alternative α-kleisin Rec8 instead of Scc1. In some organisms, meiotic cohesin complexes contain additional alternative subunits, including the Smc1 paralogue Smc1β and the Scc3 paralogues SA3 (also known as STAG3) in vertebrates and Rec11 in fission yeast.

Biochemical analyses have shown that the kleisin N terminus binds to the head domain of Smc3 and the C terminus binds to Smc1. The kleisin subunit associates with Scc3.

Condensin

Two paralogous condensin complexes — condensin I and condensin II — have been identified in many metazoans. Both condensins contain a heterodimer of SMC2 and SMC4 but associate with a distinct set of non-SMC subunits. Many fungi have a single condensin complex, which is most similar to condensin I of metazoans. In *Caenorhabditis elegans*, a third condensin-like complex —the dosage compensation complex (DCC, shown in the figure as condensin I^{DC}) — regulates the expression of X-linked genes. This complex differs from condensin I by a single subunit: the SMC2 orthologue MIX-1 forms a heterodimer with the DCC-specific SMC4 orthologue DPY-27.

Reconstitution studies have shown that the N terminus of human CAP-H binds to SMC2 and CAP-D2 but not to SMC4 or CAP-G[106]. Conversely, the C terminus of CAP-H binds only SMC4, and CAP-G, CAP-D2 and CAP-G interact only weakly *in vitro* and are therefore likely to bind CAP-H independently of one another. A similar complex architecture has been established for condensin II.

Other eukaryotic SMC complexes

In most eukaryotes, an SMC complex composed of SMC5 and SMC6 and several associated non-SMC subunits functions in DNA repair. In addition, RAD50, a subunit of the MRN (Mre11–Rad50–Nbs1) complex, also shares similarity with SMC proteins and is involved in DNA repair.

CCCTC-binding factor
A zinc-finger protein associated with diverse context-dependent effects on transcription.

Insulator
A genetic boundary element that limits the distance over which regulatory signals can act.

Chromosome conformation capture
A method for identifying physical interactions between distant DNA sequences.

cohesin and condensin in the formation of *cis* and *trans* chromosomal interactions during interphase.

Cohesin in interphase genome organization. Research on the interphase roles of cohesin was invigorated by the discovery that cohesin-binding sites in human cells largely coincide with those of CCCTC-binding factor (CTCF)[5–8], although this is not the case in *Drosophila melanogaster*[9]. CTCF is an enhancer-blocking insulator protein that promotes the formation of DNA loops that are thought to constrain interactions between promoter and enhancer elements. CTCF also promotes *trans* interactions between non-allelic loci[10] and may therefore have widespread roles in genome organization[11]. Recent data from chromosome conformation capture (3C) experiments have shown that cohesin contributes to CTCF-dependent DNA looping, at least for the small number of sites tested[12–15]. Therefore, cohesin may form topological linkages between different sites on the same DNA molecule in addition to the linkages between sister chromatids that mediate SCC. However, the effect of cohesin depletion on loop formation varies in magnitude among tested sites, which may reflect locus-specific differences in the requirement for cohesin in loop formation and/or

Box 2 | **Mitotic functions of condensin and cohesin**

In all organisms, cellular proliferation requires that the genome be replicated and then transmitted faithfully from the single parental cell to the two daughter cells during cell division. The mitotic functions of condensin and cohesin are conserved throughout eukaryotes and are crucial for accurate chromosome segregation during mitosis.

Cohesin tethers replicated chromatids together

In every cell cycle, each chromosome is replicated in S phase to form two identical sister chromatids, which are held together by sister chromatid cohesion (SCC). SCC is mediated by the cohesin complex, which associates with chromosomes before their replication and is converted into a cohesive state as replication forks pass. Therefore, sister chromatids are held together by SCC continuously from the time of their formation until their separation during mitosis. Sister chromatids separate during anaphase of mitosis when the kleisin subunit is proteolytically cleaved by separase, therefore eliminating SCC and allowing sister chromatids to be pulled to opposite spindle poles by microtubule-dependent forces. Mutation of any subunit of cohesin disrupts SCC, resulting in aneuploidy due to inaccurate chromosome segregation.

Condensin facilitates sister chromatid separation

Once cohesin is destroyed, sister chromatids can separate only if catenations between them are resolved. Moreover, chromosomes must become compacted to a volume that is small relative to the diameter of the cell. Condensin helps to fulfil these requirements. In most organisms, disrupting any condensin subunit slows the rate and/or reduces the extent of chromosome compaction during mitosis. However, the most obvious phenotype of condensin mutants is the formation of DNA bridges between chromosomes during their separation in anaphase. These anaphase bridges are widely thought to occur because of persistent topological linkages between sister chromatids, but might alternatively result from premature decompaction[3].

variation in the efficiency of RNAi knockdown in different cell types. CTCF depletion does not obviously affect SCC or the total quantity of chromosomally bound cohesin but rather disrupts cohesin accumulation at known insulator sites and other CTCF-bound sites genome-wide[5,6]. Therefore, CTCF may serve primarily to position cohesin complexes once loaded[2]. The links among CTCF, cohesin and interphase chromosome structure have been extensively reviewed[2,11,16].

Although the majority of CTCF-binding sites in mammalian cells are also occupied by cohesin[5–7], a substantial fraction of cohesin binding occurs independently of CTCF in differentiated human cells[17]. Analysis of two human cell lines found that many such sites occurred at tissue-specific genes and colocalized with binding sites for known master regulators of tissue-specific expression, such as the oestrogen receptor (ER)-α[17]. The established role of the ER in chromosome looping[18], combined with correlative evidence that cohesin preferentially binds to the base of ER-mediated loop anchors[17], supports the existence of CTCF-independent roles for cohesin in the formation of intrachromosomal loops.

Suggestions of SCC-independent roles for cohesin also arose from genetic screens in budding yeast that identified mutant alleles of *SMC1* and *SMC3*. These mutations caused chromatin silencing to spread beyond heterochromatin barrier elements (BOX 3) flanking the silent mating-type locus *HMR*[19]. 3C experiments suggested that these barrier elements interact to form the stem of a chromosomal loop that contains the silent mating-type locus[20]. Whether cohesin stabilizes this loop structure is unknown.

Condensin in interphase genome organization. Genes that function in related processes often occupy similar regions of the nucleus even though they are widely dispersed throughout the genome[21]. The best example is the nucleolus. Recent studies have shown that RNA polymerase III (RNAPIII)-transcribed tDNA loci cluster at the nucleolus[22,23]. This clustering has a major impact on the spatial organization of the genome. For example, in budding yeast, the 274 tDNA genes are distributed throughout the 16 chromosomes but predominantly associate with the nucleolus. Condensin binds all yeast tDNA genes[24,25], and disruption of any condensin subunit causes the dispersal of tDNA clusters and infrequent association with the nucleolus. Chemical inhibition of RNAPIII transcription has little effect on condensin binding to tDNA loci, showing that RNAPIII transcription itself is not necessary for condensin accumulation at these sites[25]. Instead, condensin may be recruited to these loci by subunits of the RNAPIII holocomplex, such as transcription factor IIIB (TFIIIB) and TFIIIC, which interact with condensin components independently of DNA[22]. TFIIIC binds to B-box elements (GTTCxAxxC) at RNAPIII promoters, and the introduction of an ectopic B-box motif into the budding yeast genome generated a new condensin-binding site[25]. TFIIIC has also been implicated in tDNA clustering in fission yeast[26]. Therefore, recruitment of condensin to TFIIIC-binding sites may facilitate tDNA clustering in the nucleolus by establishing or maintaining interchromosomal interactions among RNAPIII-transcribed loci. Such interactions could conceivably arise either through a single complex trapping dispersed sites or through the aggregation of complexes bound at dispersed chromosomal sites. Condensin has also been implicated in termination of DNA replication and in maintenance of genome integrity in the nucleolar organizer region that contains ribosomal DNA repeats[27,28].

In fission yeast, TFIIIC binds to a number of B-box elements independently of polymerase subunits and thereby functions to partition the genome into distinct chromatin domains by bringing the elements into proximity with each other at the nuclear periphery[29]. Whether this involves condensin is not known. In addition, Scc2, a protein required for normal chromosomal association of cohesin and condensin (see below), is involved in tDNA clustering and the relocalization of inducible RNAPII-transcribed genes to the nuclear periphery upon activation in budding yeast[30]. If these roles of TFIIIC and Scc2 occur through the action of condensin and/or cohesin, the involvement of these complexes in organizing chromatin in the nucleus is more general than previously appreciated.

Although the studies discussed above implicate condensin in promoting physical interactions between loci both in *cis* and in *trans*, recent evidence suggests that condensin inhibits other interactions. Mutations in several subunits of *D. melanogaster* condensin II enhance transvection, which suggests that condensin normally limits interactions between homologues during interphase[31]. Supporting this interpretation, *D. melanogaster* condensin II subunits are also required for the

Nucleolus
A subnuclear region in which components of the translational machinery are synthesized. It is a site of abundant transcription by RNA polymerase I and III.

Transvection
The ability of a gene on one chromosome to influence the activity of an allele on the opposite chromosome when the chromosomes are paired.

Polytene chromosomes
DNA structures containing many paired sister chromatids, which are produced by multiple rounds of DNA replication without cell division.

Supercoils
Twists applied to DNA that can occur in the same (positive) or opposite (negative) orientation to the double helix.

programmed disassembly of polytene chromosomes into unpaired chromatids, which occurs in interphase during ovarian nurse-cell development[31]. It is unknown whether condensin I acts similarly.

Collectively, these data show that during interphase, condensin both promotes clustering of dispersed loci into subnuclear domains and inhibits associations between homologues. In the latter case, parallels can be drawn with the mitotic role of condensin in preventing DNA entanglements between segregating chromosomes. This mitotic role is thought to involve the introduction of positive supercoils to compact chromosomes, which raises the possibility that the inhibition of *trans* interactions during interphase could occur by a related mechanism.

SMC complexes in gene expression

The findings outlined above demonstrate the roles of condensin and cohesin in establishing the proper architecture of interphase chromosomes. The impact of chromosome topology has been most extensively studied in the context of gene expression, although chromosome architecture is likely to influence a wide range of interphase processes.

Dosage compensation in Caenorhabditis elegans: a role for condensin. The initial indication that a condensin complex could regulate gene expression came from analysis of *Caenorhabditis elegans* dosage compensation[32–34] (FIG. 1). Dosage compensation modulates gene expression across an entire sex chromosome and is therefore a paradigm for long-range gene regulation. The *C. elegans* dosage compensation complex (DCC) is homologous to condensin but differs from condensin I by a single subunit, the SMC-4 paralogue DPY-27 (BOX 1). This change of subunit radically alters the biological function of condensin, although the underlying molecular mechanism may turn out to resemble that of classical condensin.

Box 3 | **The higher-order structure of interphase chromosomes**

The notion that eukaryotic chromosomes are organized in a non-random manner in the nucleus has become widely accepted. At the subchromosomal level, the interphase genome is organized into domains of two broad classes. Euchromatin replicates early, contains genes that are actively transcribed by RNA polymerase II and tends to occupy central positions in the nucleus. Heterochromatin replicates late, includes centromeres and repeated sequences and occupies nuclear compartments that are more peripheral. Heterochromatin-associated proteins have the ability to spread outwards along the DNA fibre by the sequential modification of histone tails to create new binding sites on adjacent nucleosomes. Similarly, activating signals emanating from transcriptional enhancers in euchromatin can potentially exert inappropriate influences on nearby genes. For these reasons, domain boundaries are demarcated by insulator elements — binding sites for proteins that physically limit the range over which regulatory signals can act.

Insulators can be divided into two subclasses, largely as a consequence of the methods by which they have been defined[107]. These subclasses are heterochromatin barriers, which inhibit the ability of heterochromatin-associated proteins to spread, and enhancer blockers, which inhibit physical contacts between enhancers and promoters. Despite the different methods used in their identification, there is evidence that insulators of both subclasses can act through interactions with other nuclear structures to regulate DNA loop formation, thereby partitioning the genome into domains of co-regulated genes.

Unlike *C. elegans* condensin I and II, the DCC is controlled by a developmental switch that regulates sex determination and coordinates gene expression across the X chromosome in response to the primary sex-determination signal: the ratio of X chromosomes to sets of autosomes (FIG. 1a). At least five additional proteins associate with the DCC condensin subunits to facilitate their loading onto both hermaphrodite X chromosomes, where gene expression is repressed by half to achieve parity with the male, which has a single X chromosome (FIG. 1a,b). DCC disruption causes increased expression of a subset of X chromosome genes in XX embryos[35].

Two distinct classes of DCC-binding sites were revealed by the combination of two approaches. Chromatin immunoprecipitation followed by microarray analysis (ChIP–chip) identified DCC-binding sites genome-wide[35,36] (FIG. 1c), and functional assays *in vivo* identified the subset of DCC-binding sites that recruit the DCC when detached from the X chromosome[35,37] (FIG. 1d). Recruitment elements on X (*rex*) sites recruit the DCC in an autonomous, DNA sequence-dependent manner through a 12-bp motif called motif enriched on X (MEX) (FIG. 1e). Approximately 200 *rex* sites confer X chromosome specificity to the dosage compensation process. However, most sites bound by the DCC at their native location on X fail to recruit the complex when detached from X. They are called dependent on X (*dox*) sites[35]. The MEX motif is enriched in *rex* sites relative to *dox* sites and on X chromosomes relative to autosomes, consistent with a role for this motif in directing the DCC to recruitment sites on X chromosomes. However, some *rex* sites lack strong MEX motifs, indicating that additional features enable those sites to recruit the DCC. Motif searches have not identified a compelling motif that distinguishes *dox* sites from random X chromosomal or autosomal DNA. The prevailing model is that *cis* linkage to *rex* sites allows *dox* sites to become fully occupied by the DCC[35,38] (R. Pferdehirt and B.J.M., unpublished observations).

Interestingly, *dox* sites are found preferentially at highly transcribed promoters, whereas *rex* sites occur more frequently at intergenic locations. DCC binding to *dox* sites in promoters is directly correlated with the expression level of the gene[35]. Furthermore, promoters that are dynamically regulated during development bind the DCC at higher levels during periods of transcriptional activity, which further implicates transcription in DCC binding to *dox* sites[38] (W. Kruesi and B.J.M., unpublished observations). By contrast, binding to *rex* sites remains relatively constant throughout somatic development. It is unknown whether this dynamic DCC-binding property reflects a direct involvement of the transcriptional machinery in determining DCC distribution, as proposed for cohesin in yeast[39].

As expected from cytological observations, ChIP–chip studies revealed that the number of DCC-binding sites on X greatly exceeded that on individual autosomes, and autosomal binding sites are occupied by the DCC less frequently[35]. Throughout the genome, the DCC accumulates at promoters of highly expressed genes transcribed by RNAPII and RNAPIII, including genes

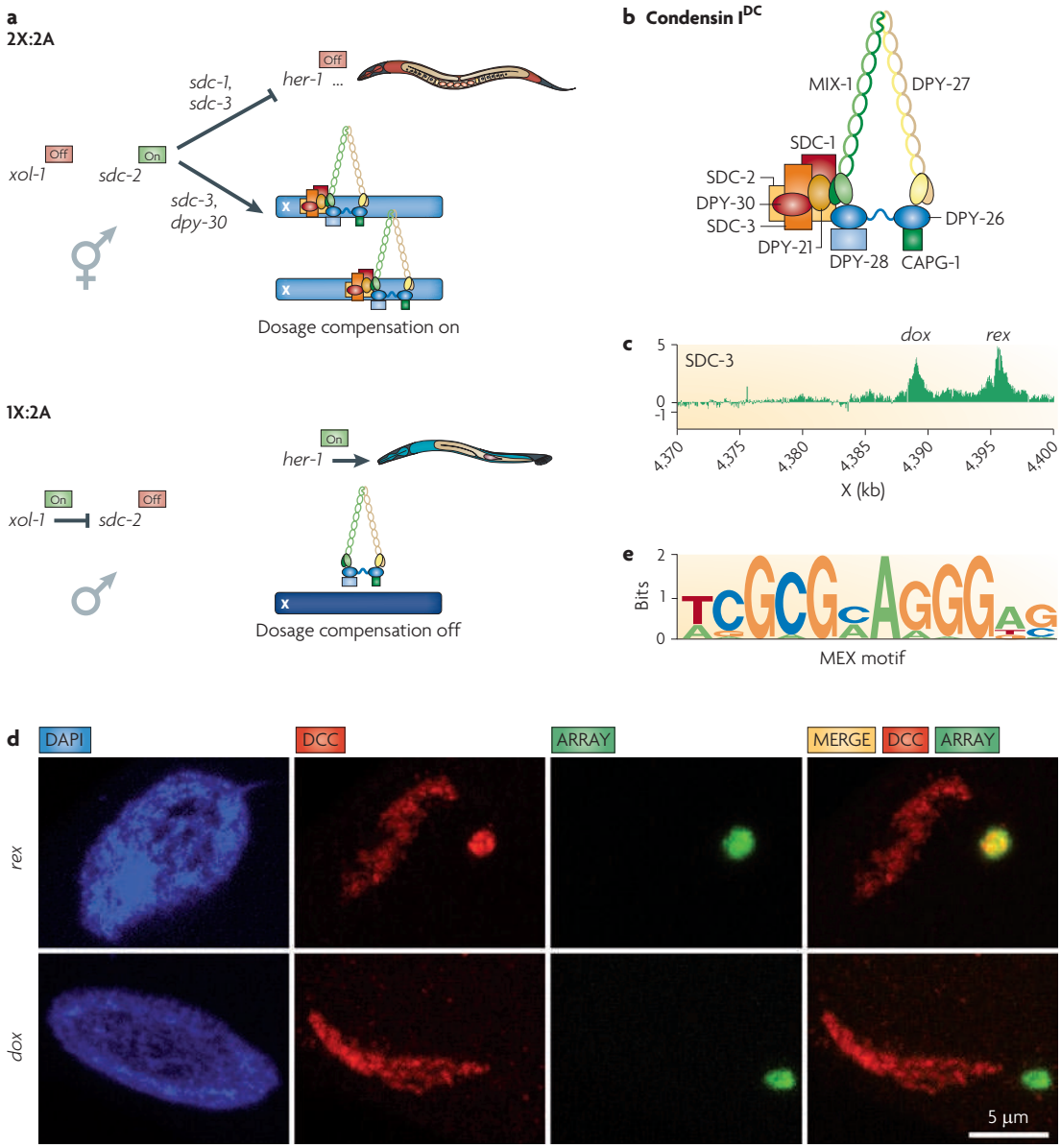


Figure 1 | **Dosage compensation in *Caenorhabditis elegans*. a** | In *Caenorhabditis elegans*, a regulatory hierarchy controls both dosage compensation and sex determination in response to the primary sex determination signal, the X:A (autosome) ratio[33]. Low ratios (for example, 1X:2A) activate the master switch gene XO lethal 1 (*xol-1*), which promotes male sexual development and inhibits dosage compensation[123,124]. High ratios (for example, 2X:2A) silence *xol-1*, thereby promoting hermaphrodite sexual development and the activation of dosage compensation. *xol-1* repression permits the XX-specific gene sex and dosage compensation 2 (*sdc-2*) to be active. SDC-2 acts with SDC-3 and DPY-30 to trigger assembly of a dosage compensation complex (DCC) onto multiple sites along X chromosomes to bring about a 50% reduction in gene expression[125]. SDC-2 acts with SDC-1 and SDC-3 to induce hermaphrodite development by binding to the autosomal male-fate-promoting gene hermaphrodization 1 (*her-1*) to repress its expression ~20-fold[126]. **b** | The DCC (shown in the figure as condensin I^{DC}) consists of five condensin-like components and at least five additional factors, which confer X- and sex-specificity[33,104]. **c** | DCC-binding sites have been mapped by chromatin immunoprecipitation followed by microarray analysis (ChIP–chip), as shown here for mapping of SDC-3 binding on the X chromosome, and have been classified into two categories by functional analysis[35]: recruitment elements on X (*rex*) sites and dependent on X (*dox*) sites. **d** | Confocal images of intestinal cell nuclei stained with the DNA dye 4,6-diamidino-2-phenylindole (DAPI) (blue), antibodies to the DCC subunit DPY-27 (red) and a fluorescence *in situ* hybridization probe that labels extrachromosomal arrays, which contain multiple copies of *rex* or *dox* sites (green). The *rex* sites robustly bind the complex when they are detached from X and are present in multiple copies on extrachromosomal arrays or integrated onto autosomes at low copy numbers. *dox* sites fail to bind the DCC when detached and must therefore depend on a broader X chromosomal context for their ability to associate with the DCC. **e** | A 12-bp consensus motif (motif enriched on X (MEX)) is enriched in *rex* sites relative to *dox* sites and on X chromosomes relative to autosomes[35]. Mutations in the motif disrupt the ability of *rex* sites to recruit the DCC. Panels **c** and **e** are modified, with permission, from REF. 25 © (2008) Cold Spring Harbor Press.

encoding tRNAs, histones and ribosomal subunits[35]. Yeast condensin also associates with ribosomal protein and tRNA genes[25], which suggests that common mechanisms may govern condensin distribution in diverse eukaryotic taxa.

Given the role of condensin in mitotic chromosome compaction, DCC-dependent repression of the X chromosome could theoretically involve localized compaction of DCC-bound promoters to limit the accessibility of transcription-factor-binding sites[36]. However, transcriptome studies of XX, XO and XX DCC mutant embryos do not support models in which the DCC only functions locally[35]. DCC binding to the promoter or coding region of a gene is not predictive of whether it will be dosage compensated. Instead, both compensated and non-compensated genes can be bound by the DCC or remain unbound, indicating that factors other than direct DCC binding help to determine whether a gene is subjected to dosage compensation. Any mechanistic model of gene regulation by the DCC must account for these findings.

The absence of DCC binding at promoters of some dosage-compensated genes may be explained if the DCC has long-range regulatory effects, perhaps through altering higher-order chromosome structure to control interactions between dispersed regulatory elements. In this model, DCC bound at some distance from regulatory targets might, by analogy to insulators, establish sex-specific domain boundaries that limit the ability of regulatory signals to influence transcription. The ability of some X-linked genes to escape dosage compensation despite the presence of DCC at the promoter might also be explained by models that involve long-range gene regulation by the DCC. Alternatively, additional regulation might be necessary for the function of some chromosome-bound complexes.

Further examples of condensin in gene regulation. Studies of position effect variegation (PEV) have implicated condensin in regulating the ability of heterochromatin to silence RNAPII transcription of nearby reporter genes in *D. melanogaster*[40,41]. Condensin components can either suppress or enhance PEV depending on the mutant allele, reporter gene and genomic location of the heterochromatin region being assayed[40,41]. This variability may reflect the non-uniform pattern of condensin binding throughout the genome[40].

The possibility that condensin can repress RNAPII transcription is further supported by the finding that mutations that disrupt individual subunits can alleviate silencing at the yeast mating-type loci[42] and homeotic genes in *D. melanogaster*[43]. The mechanisms underlying these silencing effects are unknown.

Cohesin in transcription termination. Although transcription is highly regulated at the levels of initiation and elongation, transcriptional termination efficiency can also profoundly affect both protein expression[44] and transcriptional interference between adjacent genes[45]. The loading of fission yeast cohesin between convergently transcribed gene pairs during late G1 phase has recently been shown to prevent read-through transcription during G2 phase[46] (FIG. 2a). Cohesin may function as a 'roadblock' that impedes RNAP elongation during G2 to allow the recognition of upstream cleavage sites by the 3′-end-processing machinery. Although only two loci have been examined in detail, the recent identification of several hundred cohesin-binding sites between convergently transcribed genes[47] suggests that this mechanism occurs on a wider scale in yeasts. However, cohesin enrichment between convergent genes has not been reported in metazoan genomes[5,6,48].

Cohesin in promoter–enhancer interactions. The discovery that CTCF contributes to the chromosomal positioning of cohesin in mammalian cells suggested that cohesin might participate in CTCF-dependent DNA looping and insulator functions. This hypothesis was recently tested at a well-studied enhancer-blocking insulator situated in the mammalian insulin-like growth factor 2 (*IGF2*)–*H19* domain, which is regulated by genomic imprinting (FIG. 2b). Cohesin binds several discrete sites at this locus, including the imprinting control region (ICR) — an element between *IGF2* and *H19* that contains previously characterized CTCF-binding sites. The ICR is subject to CpG methylation only on the paternal allele. CTCF and cohesin bind only the unmethylated maternal allele, resulting in allele-specific chromosome looping that impedes long-range *cis* interactions between the *IGF2* promoter and enhancer elements downstream from *H19* (REFS 6,15) (FIG. 2b). Therefore, expression occurs exclusively from the paternal allele[49,50]. RNAi-mediated depletion of cohesin destabilized CTCF-dependent loop structures, resulting in biallelic *IGF2* expression[15]. However, the low levels of *IGF2* expression in the human cell line studied mean that additional experiments are needed to assess the relative contribution of CTCF and cohesin to loop formation and gene expression at this locus.

SMC complex function in metazoan development

The results described above have shown the involvement of condensin and cohesin in regulating the interrelated processes of genome organization and gene expression. A growing body of data reveals the importance of these activities for developmental processes, including differentiation, cell-fate patterning and neuronal development.

Developmental defects from cohesin disruption. The importance of cohesin for metazoan development became evident from the body-patterning defects caused by heterozygous mutations in *Nipped-B*, a fly homologue of the cohesin loading factor Scc2 (REF. 51). More recently, the human developmental disorder Cornelia de Lange syndrome (CdLS) was shown to result from heterozygous mutations in SCC2 or the cohesin subunits SMC1A and SMC3 (REF. 52). These mutant phenotypes might result from aberrant regulation of gene expression rather than SCC defects, which have not been observed. Indeed, *Nipped-B* alleles disrupt the regulation of homeotic gene expression during wing development[51,53].

Position effect variegation
Variegated expression patterns that arise owing to intercellular differences in epigenetic gene silencing, typically observed when reporter genes are brought into proximity with heterochromatin.

Genomic imprinting
Epigenetic marks that are differentially established during male and female gametogenesis and lead to allele-specific gene expression after fertilization.

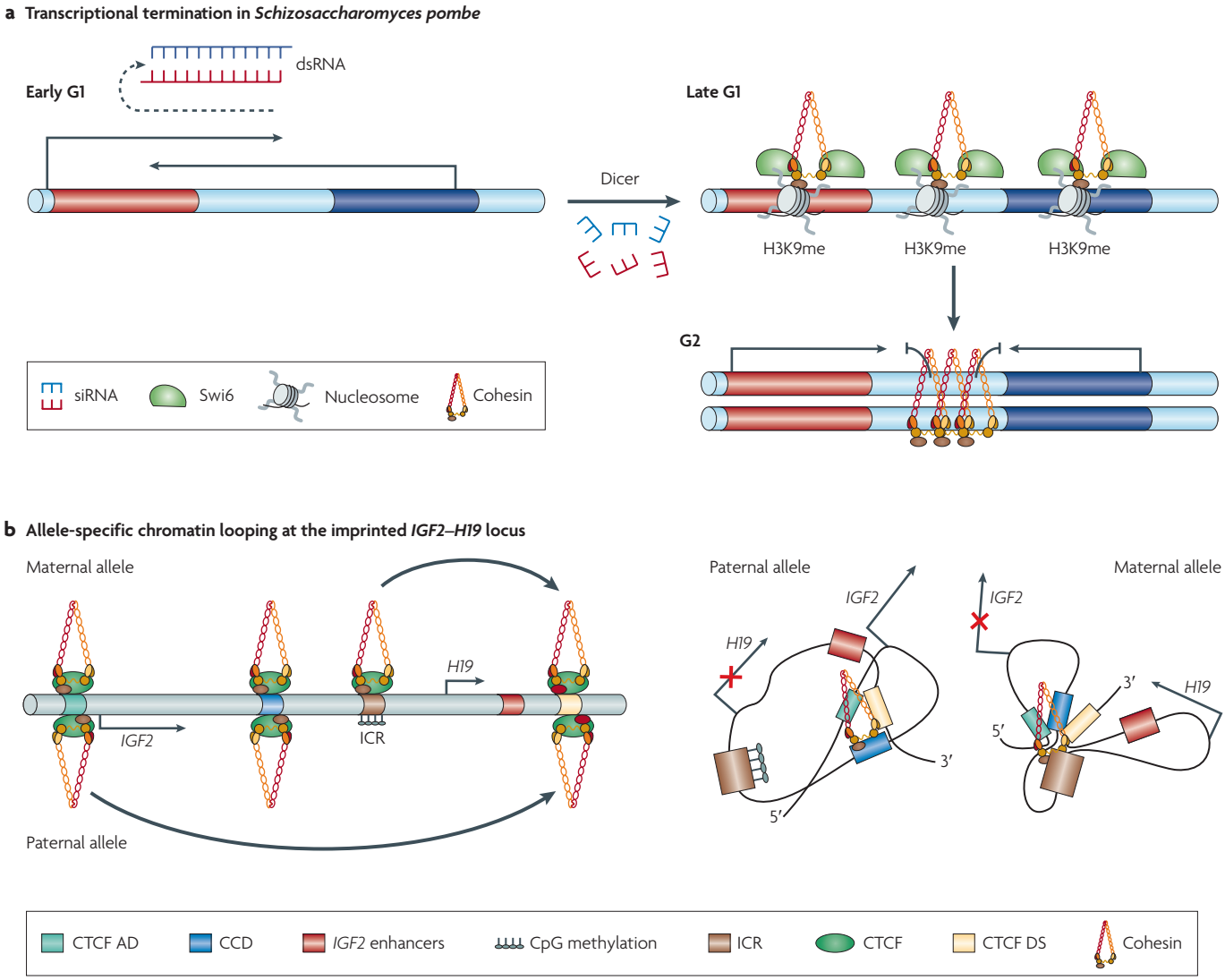


Figure 2 | **Cohesin function in gene expression. a** | Cell-cycle-dependent control of 3′-end processing in fission yeast. During the G1 phase of the cell cycle, read-through transcription from convergently transcribed gene pairs generates overlapping transcripts, which are cleaved to small interfering RNAs (siRNAs) by Dicer to induce localized transient heterochromatin formation (represented in the figure by nucleosomes marked with histone 3 lysine 9 methylation (H3K9me)) specifically during G1/S phase. Cohesin is then recruited to these sites through an interaction with the heterochromatin-associated protein Swi6. During G2, cohesin promotes the use of upstream transcriptional termination sites, preventing read-through transcription and further dsRNA formation. Cohesin removal during mitosis re-establishes read-through transcription and the cycle is repeated[46]. **b** | Allele-specific chromatin looping at a human imprinted locus. *H19* and insulin-like growth factor 2 (*IGF2*) are linked imprinted genes that are expressed from only the maternal (above chromosome) and paternal (below chromosome) alleles, respectively. The imprinting control region (ICR) situated between the two genes coordinates allele-specific expression patterns and acquires allele-specific CpG methylation during male and female gametogenesis, a pattern that is maintained in somatic tissues following fertilization. Allele-specific chromatin immunoprecipitation (ChIP) assays identified biallelic (maternal and paternal) binding of CCCTC-binding factor (CTCF) and cohesin to a region (CTCF AD) adjacent to the *IGF2* promoters, to the central conserved domain (CCD) and to a region (CTCF DS) downstream of the *IGF2* enhancers. Chromosome conformation capture (3C) experiments identified maternal-specific and paternal-specific physical interactions among these sites. On the maternal allele, CTCF and cohesin bind to the unmethylated ICR, coincident with the establishment of a DNA loop containing the *H19* gene and downstream *IGF2* enhancers. This loop is thought to sequester the enhancers from activating *IGF2*. On the paternal allele, CpG methylation at the ICR prevents CTCF and cohesin binding, leading to a distinct loop structure that allows *IGF2* to interact with the enhancers, thereby activating expression. For clarity, interactions between CTCF/cohesin-binding sites that occur at comparable levels on both alleles are not shown in the left panel. The right panel depicts a schematic model for allele-specific chromosome conformation at this locus, based on 3C data from REF. 15. For simplicity, a single cohesin complex represents all cohesin and CTCF binding in the right panel, although the number of distinct complexes bound to these sites is not known.

Cohesin in immune-cell differentiation. Mechanistic insights into the developmental roles of cohesin and CTCF came from studies of helper T (T_H) cell differentiation, an *ex vivo* model of development. Upon differentiation of naive, non-polarized CD4 T cells into C-C chemokine receptor type 5 (CCR5)-positive T_H1 cells, the interferon-γ (*IFNG*) locus becomes 'poised' for expression in response to infection. The poised state is associated with reduced DNA methylation and the emergence of DNase-hypersensitive sites at the *IFNG* locus. CTCF and cohesin binding increase at three hypomethylated, DNase-hypersensitive sites in T_H1 cells: the *IFNG* promoter and two evolutionarily conserved enhancer sequences situated 63 kb upstream and 119 kb downstream[12]. 3C experiments demonstrated a substantially higher frequency of long-range *cis* interactions between the promoter and each enhancer element in T_H1 cells relative to T_H2 or naive CD4 T cells that do not express *IFNG*. Depletion of the cohesin α-kleisin subunit in T_H1 cells greatly reduced the frequency of these long-range *cis* interactions, which resulted in lower levels of basal and inducible *IFNG* expression[12]. Cohesin and CTCF also regulate the formation of chromosome loops and the transcription of several genes in the human apolipoprotein B cluster[14], suggesting that cohesin-dependent DNA looping may be a general feature of domain-scale gene regulatory mechanisms. In both of the aforementioned studies, cohesin depletion had more profound effects on loop formation than gene expression. This may be explained if cohesin depletion destabilizes promoter–enhancer interactions, but their transient, stochastic occurrence can still substantially influence gene expression.

Cohesin in neuronal development: novel approaches. Although *ex vivo* models, such as T_H cell differentiation, are tractable for studies of mechanisms that alter genome organization to establish lineage-specific gene-expression patterns, *in vivo* approaches to address the roles of condensin and cohesin in development have been hampered by the requirement for these proteins in mitosis. Two elegant studies have taken novel approaches to assess the role of cohesin in neuronal development *in vivo*. The terminally differentiated state of neurons makes them ideally suited for studies of interphase functions of essential mitotic proteins.

In one study, transgenic fruitflies were generated with a tobacco etch mosaic virus protease (TEV^{Pr})-cleavage site in α-kleisin[54]. TEV^{Pr}-mediated cleavage reduced levels of chromosome-bound cohesin and caused massive defects in chromosome segregation and lethality. Unexpectedly, TEV^{Pr} induction specifically in postmitotic neurons disrupted axon pruning and impaired locomotion. Because these cells do not cycle, these results suggest that SCC-independent functions of cohesin during interphase might be vital for normal metazoan development[54].

An independent study also implicated cohesin in developmentally regulated axon pruning and showed that this cohesin function involves the regulation of gene expression[55]. Alleles of the cohesin subunits *Smc1* and *Scc3* were identified in a forward genetic screen for factors required for axon pruning in *D. melanogaster* mushroom bodies. This screen involved the use of *piggyBac* transposons to create genetic mosaics, thereby circumventing embryonic lethality arising from chromosome segregation defects. Expression of a wild-type *Smc1* transgene specifically in postmitotic cells rescued the axon-pruning defects of *Smc1* mutants. This role of cohesin may therefore be independent of SCC. The axon-pruning phenotypes of cohesin mutants resembled those seen following disruption of the Ecdysteroid receptor (ECR), a known master regulator of developmental axon pruning. Cohesin-binding sites were identified at the *Ecr* locus[48], and mutations in *Smc1* and *Scc3* dramatically reduced ECR protein levels[55]. Given the roles of cohesin at the *IFNG* and *IGF2* loci, described above, cohesin might establish intrachromosomal associations that promote ECR expression during interphase.

Condensin in lymphocyte development. A role for condensin in the acquisition of cell-lineage-specific traits is shown by the *nessy* mouse[56]. *Nessy* mice are homozygous for a point mutation causing a single amino acid change in the alternatively spliced but highly conserved first exon of the gene that encodes CAP-H2[57]. The mice have a defect in T cell lymphocyte development that results in lower numbers of circulating T cells and reduced antibody production[56] but lack other obvious abnormalities, even in the parallel pathway of B cell differentiation. Whether this variant CAP-H2 influences transcription during normal T cell development is unknown.

Condensin and cohesin in meiosis

Specialized functions of condensin and cohesin abound in meiosis, the cell division program that reduces ploidy during gametogenesis or sporulation (BOX 4). Here, we briefly discuss requirements for cohesin and condensin that are shared in mitotic and meiotic nuclei and then focus on meiosis-specific roles.

Meiotic roles of cohesin. Shortly after cohesin was implicated in mitotic SCC[58–60], work in yeast showed cohesin to be essential for meiotic SCC[61]. Disrupting Smc3 during meiosis causes premature sister separation. However, *scc1* mutations do not cause this defect, because the α-kleisin Rec8 replaces Scc1 in meiotic cohesin complexes. This substitution is crucial for stepwise separation of homologues and then sister chromatids[62,63] and seems to be conserved among eukaryotes.

Studies in yeast also showed that Rec8-containing cohesin complexes (Rec8 cohesin)[61], but not SCC[64,65] are required for axial element (AE) assembly, synapsis and crossover (CO) recombination: events that are unique to meiosis and required to reduce ploidy (BOX 4). Surprisingly, Rec8 is not essential for AE assembly in many higher eukaryotes[66–69], which suggests that cohesin is not universally important for AE assembly[70]. However, the recent discovery of meiotic roles for REC-8 paralogues in *C. elegans* has challenged that view[71]: REC-8 and the nearly identical kleisins COH-3 and COH-4 (REFS 71,72) all function in meiotic SCC, but

Axon pruning
The selective loss of neuronal outgrowths to refine synaptic connectivity during development.

Genetic mosaics
Animals in which homozygous mutations are carried by only a small clone of cells.

Axial elements
Linear structures that assemble along the length of meiotic chromosomes. Axial elements become the lateral elements of the mature synaptonemal complex.

Co-orient
Attach to microtubules from the same spindle pole.

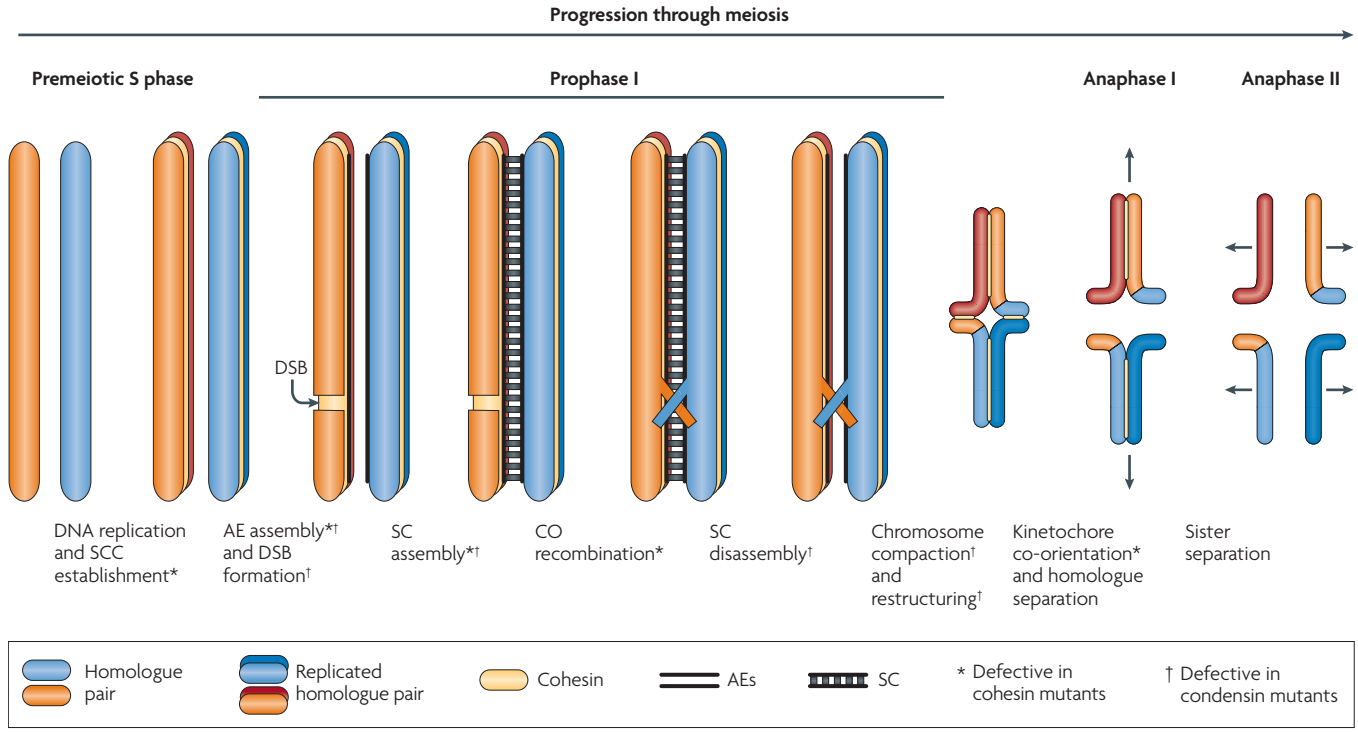
Bi-orient
Attach to microtubules from opposite spindle poles.

severe defects in SCC and AE assembly occur only in mutants that lack all three kleisins or are depleted for SMC-1 or SCC-3, which are integral to all worm cohesin complexes[71,73,74]. Therefore, cohesin is essential for AE assembly in *C. elegans*, but that requirement was obscured by the involvement of multiple kleisins.

Studies in other organisms have identified multiple Rec8 paralogues and are consistent with multiple meiotic cohesin complexes having distinct kleisin subunits. SCC persists in *rec8* mutants in *Arabidopsis thaliana,* maize and mice[66,68,75,76], and SMC1 associates with meiotic chromosomes of mouse *Rec8* mutants[66,76]. Discerning how cohesin complexes with different subunit compositions collaborate to control meiotic chromosome behaviours is a crucial topic for future research.

Meiotic roles of condensin. The involvement of condensin in meiosis was first demonstrated in *C. elegans*. SMC-4 and the SMC2 orthologue MIX-1 associate with the centromeric histone variant CENP-A on chromosomes during meiosis and mitosis[77], and depleting condensin disrupts meiotic chromosome compaction and resolution, which results in chromatin bridges during anaphase I and II[77,78]. Similar meiotic defects have since

Box 4 | **The events of meiosis reduce ploidy**



Unlike mitosis, which results in the production of two cells that are genetically identical to their single precursor, meiosis produces cells (gametes or spores) that contain exactly half of the genetic material of the precursor cell. A scheme of meiosis is shown in the figure. Genome copy number is reduced through two rounds of chromosome segregation that follow a single round of DNA replication[108]. In most organisms, homologous chromosomes separate at anaphase I, whereas sister chromatids separate at anaphase II. To achieve this pattern of chromosome segregation, homologues become linked together early in meiosis to allow their accurate segregation from one another. Additional events occur later in meiosis, at or near the time of chromosome segregation, to ensure that homologues and sisters separate in two steps.

In most organisms, crossover (CO) recombination is the process that tethers homologues together. Meiotic recombination is initiated by programmed double-strand breaks (DSBs), which are catalysed by the endonuclease SPO11. These DSBs are repaired by homologous recombination pathways that are similar to those involved in DNA-damage repair in somatic cells; however, the sister chromatid is usually used as a repair template in the soma, but only repair from the homologue can generate the interhomologue linkages that are needed in the germ line for accurate segregation of meiotic chromosomes.

The processes of homologue pairing and synapsis promote the use of the homologue as a repair template. Shortly after the completion of bulk DNA replication in premeiotic S phase, structures called axial elements (AEs) assemble along the length of each meiotic chromosome and homologues pair with one another and align along their lengths. Synaptonemal complex (SC) transverse elements assemble between homologous AEs (synapsis). The mature SC holds homologues in close proximity in an extended, parallel arrangement that facilitates reciprocal exchange of DNA. Once recombination is complete, sister chromatid cohesion (SCC) around the CO holds both homologues and sisters together. The SC disassembles and chromosomes are reorganized around the CO into a compact structure in preparation for their separation in anaphase I and II.

Homologue pairing, synapsis, interhomologue CO recombination and desynapsis all occur during the extended prophase of meiosis I. However, these events alone cannot produce the meiotic pattern of chromosome segregation. The two sister kinetochores of each homologue must co-orient in meiosis I and bi-orient in meiosis II, and SCC must be released in two steps to allow the successive separation of homologues and then sister chromatids. The processes that mediate kinetochore co-orientation and regulate the release of SCC have been extensively discussed in a recent review[109].

been observed for condensin mutants of yeast, *A. thaliana* and *D. melanogaster*[79–81], and additional meiotic functions have also been discovered.

Condensin promotes synaptonemal complex (SC) assembly in yeast by facilitating the chromosome association of the AE proteins Red1 and Hop1 (REF. 81). Condensin is also crucial for the association of Cdc5 (also known as polo kinase) with yeast meiotic chromosomes[82] and the consequent phosphorylation of cohesin by Cdc5. Phosphorylation promotes the removal of a subset of cohesin during prophase I, which facilitates homologue separation at anaphase I[82]. It is likely that condensin functions as a structural element that promotes the association of factors with meiotic chromosomes, but the mechanistic relationship between this role and the functions of condensin in chromosome compaction and resolution is unknown.

In *C. elegans*, the occurrence of COs is highly regulated: only a single CO forms between each homologue pair. Two condensin complexes participate in CO regulation[83]. Mutations disrupting either complex increase the number of COs (so homologue pairs with multiple COs are common) and alter CO distribution (so specific regions of the genome have more COs at the expense of others). Importantly, mutations that disrupt the major CO-controlling complex, condensin I, and those that disrupt the minor CO-controlling complex, condensin II, have different effects on CO distribution. Therefore, condensin I and II do not perform redundant functions in CO control but together influence the recombination landscape.

Cytological analyses of recombination intermediates (RAD-51 foci) and DNA double-strand breaks (DSBs, as revealed by TUNEL (terminal deoxyuridine 5′-triphosphate nick-end-labelling) assays) showed that condensin influences CO number and distribution by regulating the number and position of programmed DSBs[83]. Moreover, the length of chromosomal axes is greatly extended (1.6-fold) in mutants in which either condensin complex is disrupted and further extended (1.8-fold) in mutants in which both complexes are disrupted. AE assembly seems to be normal in these mutants[78,83,84]. Two lines of evidence suggest that axis extension is causal to the increase in DSB number. First, axis length in *C. elegans* is unaffected by the induction of additional DSBs through gamma irradiation or the reduction of DSBs by mutation of the meiotic endonuclease SPO-11, indicating that DSB frequency does not affect axis length in *C. elegans*[83]. Second, a partial loss-of-function mutation in the high incidence of males 3 (*him-3*) gene, which encodes an AE protein, suppresses both the axis extension phenotype and the increase in RAD-51 foci in condensin mutants[83,84].

Intriguingly, the chromosomal axes of yeast condensin mutants are also extended (1.5-fold). Because axis length is normal in *hop1* mutants[81], the length increase is not a consequence of AE defects. Instead, condensin has independent roles in determining the composition and length of the chromosomal axis.

The chromatin of meiotic chromosomes is organized in a series of loops emanating from the meiotic axis. Loop density is well conserved among organisms and loop number is directly correlated with axis length[70,85,86]. It has been proposed that DSBs are formed on chromosome loops in regions distal to axis attachment points[70]. Therefore, we have suggested that *C. elegans* condensin limits the number of DSBs, and thereby the number of COs, by promoting the formation of a compact meiotic axis and therefore a relatively small number of loops[83].

SMC complex loading and distribution

SMC complexes perform their functions while bound to chromatin. In this section, we describe genetic, genomic and biochemical studies that have identified factors that are important for the loading of condensin and cohesin onto chromosomes.

Cohesin loading. In mitotically proliferating eukaryotic cells, Scc1 is cleaved by separase at anaphase onset to allow sister chromatids to separate[87,88]. Cohesin then re-associates with chromosomes, both to regulate gene expression and to prepare for DNA replication. In all systems studied, bulk cohesin loading requires a heterodimer of Scc2 and Scc4 (Scc2–Scc4), which acts through a mechanism that is not presently understood[89–92]. However, Scc2–Scc4 binds to cohesin and chromosomes independently[90,93,94] and may therefore directly recruit cohesin to chromosomes. Scc2–Scc4-independent cohesin loading has been demonstrated at mitotic centromeres in *Saccharomyces cerevisiae*, and cohesin persists at meiotic centromeres of *D. melanogaster Nipped-B* mutants, which suggests that Scc2–Scc4 is not essential for all cohesin loading[95,96]. The extent to which Scc2–Scc4-independent cohesin loading occurs remains to be determined.

Over the past decade, ChIP–chip studies have yielded insights into the distribution and specificity of cohesin binding to budding yeast chromosomes. Sites of cohesin enrichment occur on average every 15 kb and lack shared nucleotide motifs, which argues against direct sequence-dependent recruitment to these sites[39,97]. The distribution of chromosome-bound cohesin seems to be dynamic and is influenced by transcription and DNA-damage repair. Cohesin binds primarily at intergenic sites between convergently transcribed genes, and cohesin bound in coding regions of inducible genes is displaced following transcriptional activation[39,97]. Surprisingly, in G2 phase, sites of Scc2–Scc4 and cohesin binding overlapped only modestly[39], consistent with observations of discordant Scc2–Scc4 and cohesin localization on chromosome spreads[90,93]. It was therefore proposed that, after it is recruited, cohesin relocates along the chromosome, propelled by RNA polymerases until progress is blocked by a converging transcription unit[39]. However, a more recent ChIP–chip study, which used different antibodies, found that the majority of cohesin-binding sites overlapped with Scc2–Scc4 throughout the G2 phase[98], which is consistent with findings from cultured metazoan cells[48,99]. More experiments will be needed to resolve this controversy. Although transcription antagonizes cohesin accumulation in yeast[39,97,100], cohesin binds preferentially in active genes in *D. melanogaster* cells[48] and is enriched in proximity to active promoters in mammals[99].

Synaptonemal complex
A proteinaceous structure that forms between pairs of homologous chromosomes during synapsis and facilitates crossover recombination.

Separase
A cysteine protease that cleaves the α-kleisin subunit of cohesin at the onset of anaphase to allow sister chromatid disjunction.

Box 5 | **Condensin and cohesin are regulated by post-translational modifications**

Condensin and cohesin are subject to dynamic mechanisms of regulation that differ throughout the cell cycle. Several key examples of regulation by post-translational modifications are outlined below.

Cohesin acetylation promotes SCC establishment

Sister chromatid cohesion (SCC) establishment is tightly coupled to replication and some, if not all, cohesion is generated at replication forks[110]. Cohesion is established by the acetyltransferase Eco1, which acetylates at least two lysine residues in the structural maintenance of chromosomes 3 (Smc3) head region[111–114]. DNA damage in G2/M phase of the cell cycle induces SCC independently of replication[115,116]. Damage during this phase activates the serine/threonine kinase Mec1 (ATR in mammals), which in turn leads to Chk1 kinase-dependent phosphorylation of Scc1 on serine 83 (REF. 105). Consequently, Eco1-dependent acetylation of Scc1 generates SCC *de novo*, both at the break site and on undamaged chromosomes. Therefore, SCC establishment during S phase and in response to DNA damage occur through different routes. Both require Eco1-dependent acetylation of a cohesin subunit but different subunits are modified in each context.

Cohesin phosphorylation promotes the release of SCC

Separation of sister chromatids at anaphase requires cleavage of the kleisin subunit of cohesin by separase. This process is enhanced by phosphorylation of residues adjacent to the cleavage sites by Cdc5 (also known as polo kinase)[117]. During meiosis, Cdc5-dependent phosphorylation may also promote Rec8 cleavage by separase, and regulated dephosphorylation of Rec8 at meiotic centromeres may facilitate the stepwise separation of homologues and then sisters[109]. Phosphorylation by Cdc5 promotes separase-independent removal of cohesin from chromosomes during prophase I of meiosis in yeast[82], and cohesin phosphorylation by polo and aurora B-type kinases has been implicated in separase-independent dissociation of cohesin from chromosome arms during mitotic prophase in many eukaryotes[2].

Phosphorylation regulates chromosomal loading and supercoiling activity of condensin

The Cdc2 and Aurora B kinases phosphorylate all three non-SMC subunits of condensin I and are required for condensin I loading[118–120]. Aurora B is also required for loading of condensin II in *Caenorhabditis elegans*[77]. Similarly, levels of chromosomally bound condensin II were reduced following immunodepletion of Aurora B from *Xenopus laevis* extracts[120]. However, relatively normal amounts of condensin II were bound to chromosomes in Aurora B-depleted human cells, which suggests that the requirement of Aurora B for condensin II loading may not be universal[119].

Phosphorylation may regulate condensin activity as well as loading. Differential phosphorylation of condensin subunits by interphase and mitotic kinases correlates with supercoiling activity, which is high during mitosis (when chromosomes are condensed) and low during interphase (when chromosomes are decondensed)[121]. Because the mitotic kinases that upregulate supercoiling activity also promote condensin loading, elucidation of the relationship among condensin phosphorylation, chromosomal loading, supercoiling activity and chromosome condensation is likely to require a comprehensive analysis of the contribution of individual phosphorylation events. The recent demonstration of supercoiling activity for budding yeast condensin[122] means that yeast genetics can now be applied to studying the relationship between these activities.

Condensin loading. Metazoans possess at least two condensin complexes (BOX 1). With the exception of the *C. elegans* DCC, which is loaded by proteins under the control of a sex-specific developmental switch (FIG. 1), genome-wide localization data are not presently available for any metazoan condensin complex. By contrast, ChIP–chip studies of the single condensin complex in budding yeast revealed a chromosomal binding profile that is essentially unaltered throughout the cell cycle[25].

The recent, surprising demonstration of chromosome compaction defects and reduced condensin binding in budding yeast *scc2* and *scc4* mutants suggests that the Scc2–Scc4 complex might load both condensin and cohesin[25]. In this study, although condensin bound to intergenic sites with a similar periodicity to cohesin (approximately 15 kb), condensin did not accumulate preferentially between convergently transcribed genes. Deletion of sequences (8.5 kb) between the sites of condensin binding did not change the regions of condensin occupancy, which suggests that primary DNA sequences are important for directing localization. As described above, TFIIIC binding to B-box motifs seems to recruit condensin to the promoters of tRNA genes and other RNAPIII-transcribed loci. The Scc2–Scc4 complex binds these same sites, and TFIIIC disruption reduced chromosomal binding of both Scc2–Scc4 and condensin[22,25]. These data are consistent with the model in which Scc2–Scc4 loads condensin onto chromosomes. However, further experiments are needed to determine whether condensin loading is reduced by *scc2* and *scc4* mutations in other eukaryotes and to demonstrate rigorously in any organism that the reduced condensin levels are not an indirect consequence of reduced cohesin loading.

Functional diversity of SMC complexes

In this Review, we have highlighted the wide range of biological processes that involve condensin and cohesin. In this section, we discuss models of how SMC complexes might participate in diverse processes that occur simultaneously in the same nucleus. For simplicity, complex composition, post-translational modifications and environmental influences are considered separately, although their contributions to functional diversity are interrelated.

Complex composition. For both condensin and cohesin, the reshuffling of interchangeable molecular parts can create independent complexes with similar architectures but distinct functions. Studies in *C. elegans*[71] (see above)

and mice[66,76,101,102] have shown that multiple cohesin complexes with different subunit combinations and distinct functions coexist in meiotic nuclei. Similarly, condensin I and II bind chromosomes with different temporal and spatial patterns, and distinct meiotic and mitotic phenotypes result from disruption of either complex[83,84,103,104]. Changing even one condensin subunit can dramatically alter complex function. The *C. elegans* DCC differs from condensin I by a single subunit, yet the DCC is not required for mitotic chromosome segregation or meiotic crossover control, but rather for regulating X-chromosome gene expression.

Post-translational modification. SMC complex function can also be specified through post-translational modifications (BOX 5). An elegant study in yeast[105] showed that the range of post-translational modifications an SMC complex can be subject to, and thereby the range of cellular functions the complex can perform, is influenced by subunit composition. Phosphorylation of serine 83 of Scc1 by Chk1 is crucial for damage-induced SCC (DI-SCC) in budding yeast (BOX 5). Rec8 lacks this serine and consequently Rec8 cohesin cannot establish DI-SCC[105]. Introducing a serine into Rec8 in the equivalent position confers the ability to establish DI-SCC, indicating that the different capacities of Scc1 cohesin and Rec8 cohesin to generate DI-SCC result primarily from a single amino acid change.

Influence of the molecular environment. The environment in which a complex resides can also influence its function. For example, cohesin associates with chromosomes at relatively normal levels following CTCF depletion, and failure to accumulate cohesin at CTCF-bound sites affects gene regulation without obvious impact on SCC. Independently of CTCF, oestrogen stimulation of breast cancer cells leads to increased cohesin binding at sites bound by ER-α[17]. An attractive model therefore posits that tissue-specific transcription factors impart cell-type specificity to the distribution of cohesin complexes in differentiated cells, thereby implementing cell-type-specific chromosome topologies. Experiments are needed to determine: whether the specific cohesin complexes that participate in insulator activity also participate in SCC; whether cohesin simultaneously binds the same stretches of DNA as factors such as CTCF or various master regulators of cell-type-specific gene expression; and the relative contribution of cohesin and cofactors, such as CTCF, towards insulator function.

Conclusions

Condensin and cohesin function in a number of processes independently of their classically defined roles, but the mechanisms that underlie these functions are poorly understood because disrupting either complex results in mitotic defects and lethality. Despite these hurdles, much has been learned through use of conditional, tissue-specific or separation-of-function alleles, as well as RNAi in cultured cells. Future studies are likely to increase our appreciation of the molecular diversity of condensin and cohesin complexes, of how each complex subtype is regulated and of the influence of molecular context on complex activity. Such detailed knowledge will be key to understanding the full repertoire of condensin and cohesin functions and may provide insights into diseases such as CdLS, which result from mutations that disrupt genes that are crucial for SCC but do not cause obvious cohesion defects.

1. De Piccoli, G., Torres-Rosell, J. & Aragon, L. The unnamed complex: what do we know about Smc5–Smc6? *Chromosome Res.* **17**, 251–263 (2009).
2. Nasmyth, K. & Haering, C. H. Cohesin: its roles and mechanisms. *Annu. Rev. Genet.* **43**, 525–558 (2009).
3. Hudson, D. F., Marshall, K. M. & Earnshaw, W. C. Condensin: architect of mitotic chromosomes. *Chromosome Res.* **17**, 131–144 (2009).
4. Hirano, T. At the heart of the chromosome: SMC proteins in action. *Nature Rev. Mol. Cell Biol.***7**, 311–322 (2006).
5. Parelho, V. *et al.* Cohesins functionally associate with CTCF on mammalian chromosome arms. *Cell* **132**, 422–433 (2008).
6. Wendt, K. S. *et al.* Cohesin mediates transcriptional insulation by CCCTC-binding factor. *Nature* **451**, 796–801 (2008).
7. Rubio, E. D. *et al.* CTCF physically links cohesin to chromatin. *Proc. Natl Acad. Sci. USA* **105**, 8309–8314 (2008).
8. Stedman, W. *et al.* Cohesins localize with CTCF at the KSHV latency control region and at cellular *c-myc* and *H19/Igf2* insulators. *EMBO J.* **27**, 654–666 (2008). **References 5–8 identified extensive overlaps between the chromosomal binding sites of cohesin and the mammalian insulator protein CTCF, and showed that cohesin contributes to the gene regulatory functions of CTCF.**
9. Bartkuhn, M. *et al.* Active promoters and insulators are marked by the centrosomal protein 190. *EMBO J.* **28**, 877–888 (2009).
10. Ling, J. Q. *et al.* CTCF mediates interchromosomal colocalization between *Igf2/H19* and *Wsb1/Nf1*. *Science* **312**, 269–272 (2006).
11. Phillips, J. E. & Corces, V. G. CTCF: master weaver of the genome. *Cell* **137**, 1194–1211 (2009).
12. Hadjur, S. *et al.* Cohesins form chromosomal *cis*-interactions at the developmentally regulated *IFNG* locus. *Nature* **460**, 410–413 (2009).
13. Hou, C., Dale, R. & Dean, A. Cell type specificity of chromatin organization mediated by CTCF and cohesin. *Proc. Natl Acad. Sci. USA* **107**, 3651–3656 (2010).
14. Mishiro, T. *et al.* Architectural roles of multiple chromatin insulators at the human apolipoprotein gene cluster. *EMBO J.* **28**, 1234–1245 (2009).
15. Nativio, R. *et al.* Cohesin is required for higher-order chromatin conformation at the imprinted *IGF2–H19* locus. *PLoS Genet.* **5**, e1000739 (2009). **References 12–15 studied the effects of cohesin depletion in cultured cells on interphase chromosome looping and transcription.**
16. Wendt, K. S. & Peters, J. M. How cohesin and CTCF cooperate in regulating gene expression. *Chromosome Res.* **17**, 201–214 (2009).
17. Schmidt, D. *et al.* A CTCF-independent role for cohesin in tissue-specific transcription. *Genome Res.* 10 Mar 2010 (doi:10.1101/gr.100479.109).
18. Fullwood, M. J. *et al.* An oestrogen-receptor-α-bound human chromatin interactome. *Nature* **462**, 58–64 (2009).
19. Donze, D., Adams, C. R., Rine, J. & Kamakaka, R. T. The boundaries of the silenced *HMR* domain in *Saccharomyces cerevisiae*. *Genes Dev.* **13**, 698–708 (1999).
20. Valenzuela, L., Dhillon, N., Dubey, R. N., Gartenberg, M. R. & Kamakaka, R. T. Long-range communication between the silencers of *HMR*. *Mol. Cell. Biol.* **28**, 1924–1935 (2008).
21. Schoenfelder, S. *et al.* Preferential associations between co-regulated genes reveal a transcriptional interactome in erythroid cells. *Nature Genet.* **42**, 53–61 (2010).
22. Haeusler, R. A., Pratt-Hyatt, M., Good, P. D., Gipson, T. A. & Engelke, D. R. Clustering of yeast tRNA genes is mediated by specific association of condensin with tRNA gene transcription complexes. *Genes Dev.* **22**, 2204–2214 (2008).
23. Thompson, M., Haeusler, R. A., Good, P. D. & Engelke, D. R. Nucleolar clustering of dispersed tRNA genes. *Science* **302**, 1399–1401 (2003).
24. Wang, B. D. & Strunnikov, A. Transcriptional homogenization of rDNA repeats in the episome-based nucleolus induces genome-wide changes in the chromosomal distribution of condensin. *Plasmid* **59**, 45–53 (2008).
25. D'Ambrosio, C. *et al.* Identification of *cis*-acting sites for condensin loading onto budding yeast chromosomes. *Genes Dev.* **22**, 2215–2227 (2008). **This paper and reference 22 provided evidence that the yeast condensin complex binds tRNA genes through interactions with the RNAPIII transcription factor TFIIIC and is required for their aggregation at the nucleolus.**
26. Iwasaki, O., Tanaka, A., Tanizawa, H., Grewal, S. I. & Noma, K. Centromeric localization of dispersed Pol III genes in fission yeast. *Mol. Biol. Cell* **21**, 254–265 (2009).
27. Tsang, C. K., Wei, Y. & Zheng, X. F. Compacting DNA during the interphase: condensin maintains rDNA integrity. *Cell Cycle* **6**, 2213–2218 (2007).
28. Kobayashi, T. Strategies to maintain the stability of the ribosomal RNA gene repeats — collaboration of recombination, cohesion, and condensation. *Genes Genet. Syst.* **81**, 155–161 (2006).
29. Noma, K., Cam, H. P., Maraia, R. J. & Grewal, S. I. A role for TFIIIC transcription factor complex in genome organization. *Cell* **125**, 859–872 (2006).

30. Gard, S. *et al.* Cohesinopathy mutations disrupt the subnuclear organization of chromatin. *J. Cell Biol.* **187**, 455–462 (2009).
31. Hartl, T. A., Smith, H. F. & Bosco, G. Chromosome alignment and transvection are antagonized by condensin II. *Science* **322**, 1384–1387 (2008).
This paper showed that the *D. melanogaster* condensin II complex inhibits transvection and promotes the disassembly of polytene chromosomes, and can therefore antagonize interactions between homologous chromosomes during interphase. These findings raise interesting parallels between condensin function during mitosis and during interphase.
32. Chuang, P. T., Albertson, D. G. & Meyer, B. J. DPY-27: a chromosome condensation protein homolog that regulates *C. elegans* dosage compensation through association with the X chromosome. *Cell* **79**, 459–474 (1994).
33. Meyer, B. J. X-Chromosome dosage compensation. In *WormBook* (ed. The *C. elegans* Research Community) http://www.wormbook.org, doi:10.1895/wormbook.1.8.1 (2005).
34. Meyer, B. Targeting X chromosomes for repression. *Curr. Opin. Genet. Dev.* 8 Apr 2010 (doi:10.1016/j.gde.2010.03.008).
35. Jans, J. *et al.* A condensin-like dosage compensation complex acts at a distance to control expression throughout the genome. *Genes Dev.* **23**, 602–618 (2009).
This paper combined ChIP–chip mapping with functional assays to identify two classes of binding sites for the *C. elegans* DCC: those that recruit the complex in an autonomous, sequence-dependent manner and those that bind the DCC only when part of an intact X chromosome. The paper also correlated DCC binding with function, providing evidence that the DCC influences transcription at long range.
36. Ercan, S. *et al.* X chromosome repression by localization of the *C. elegans* dosage compensation machinery to sites of transcription initiation. *Nature Genet.* **39**, 403–408 (2007).
37. McDonel, P., Jans, J., Peterson, B. K. & Meyer, B. J. Clustered DNA motifs mark X chromosomes for repression by a dosage compensation complex. *Nature* **444**, 614–618 (2006).
38. Ercan, S., Dick, L. L. & Lieb, J. D. The *C. elegans* dosage compensation complex propagates dynamically and independently of X chromosome sequence. *Curr. Biol.* **19**, 1777–1787 (2009).
39. Lengronne, A. *et al.* Cohesin relocation from sites of chromosomal loading to places of convergent transcription. *Nature* **430**, 573–578 (2004).
40. Cobbe, N., Savvidou, E. & Heck, M. M. Diverse mitotic and interphase functions of condensins in *Drosophila*. *Genetics* **172**, 991–1008 (2006).
41. Dej, K. J., Ahn, C. & Orr-Weaver, T. L. Mutations in the *Drosophila* condensin subunit dCAP-G: defining the role of condensin for chromosome condensation in mitosis and gene expression in interphase. *Genetics* **168**, 895–906 (2004).
42. Bhalla, N., Biggins, S. & Murray, A. W. Mutation of *YCS4*, a budding yeast condensin subunit, affects mitotic and nonmitotic chromosome behavior. *Mol. Biol. Cell* **13**, 632–645 (2002).
43. Lupo, R., Breiling, A., Bianchi, M. E. & Orlando, V. *Drosophila* chromosome condensation proteins Topoisomerase II and Barren colocalize with Polycomb and maintain *Fab-7* PRE silencing. *Mol. Cell* **7**, 127–136 (2001).
44. West, S. & Proudfoot, N. J. Transcriptional termination enhances protein expression in human cells. *Mol. Cell* **33**, 354–364 (2009).
45. Shearwin, K. E., Callen, B. P. & Egan, J. B. Transcriptional interference — a crash course. *Trends Genet.* **21**, 339–345 (2005).
46. Gullerova, M. & Proudfoot, N. J. Cohesin complex promotes transcriptional termination between convergent genes in *S. pombe*. *Cell* **132**, 983–995 (2008).
This paper demonstrated that recruitment of cohesin to sites of convergent transcription during G1 requires overlapping antisense transcription and components of the RNAi pathway. During G2, cohesin complexes promote the use of upstream transcriptional termination sites at these loci.
47. Schmidt, C. K., Brookes, N. & Uhlmann, F. Conserved features of cohesin binding along fission yeast chromosomes. *Genome Biol.* **10**, R52 (2009).
48. Misulovin, Z. *et al.* Association of cohesin and Nipped-B with transcriptionally active regions of the *Drosophila melanogaster* genome. *Chromosoma* **117**, 89–102 (2008).
49. DeChiara, T. M., Robertson, E. J. & Efstratiadis, A. Parental imprinting of the mouse insulin-like growth factor II gene. *Cell* **64**, 849–859 (1991).
50. Murrell, A., Heeson, S. & Reik, W. Interaction between differentially methylated regions partitions the imprinted genes *Igf2* and *H19* into parent-specific chromatin loops. *Nature Genet.* **36**, 889–893 (2004).
51. Rollins, R. A., Morcillo, P. & Dorsett, D. Nipped-B, a *Drosophila* homologue of chromosomal adherins, participates in activation by remote enhancers in the *cut* and *Ultrabithorax* genes. *Genetics* **152**, 577–593 (1999).
52. Liu, J. & Krantz, I. D. Cornelia de Lange syndrome, cohesin, and beyond. *Clin. Genet.* **76**, 303–314 (2009).
53. Dorsett, D. Cohesin, gene expression and development: lessons from *Drosophila*. *Chromosome Res.* **17**, 185–200 (2009).
54. Pauli, A. *et al.* Cell-type-specific TEV protease cleavage reveals cohesin functions in *Drosophila* neurons. *Dev. Cell* **14**, 239–251 (2008).
55. Schuldiner, O. *et al. piggyBac*-based mosaic screen identifies a postmitotic function for cohesin in regulating developmental axon pruning. *Dev. Cell* **14**, 227–238 (2008).
References 54 and 55 utilized novel approaches to disrupt cohesin specifically in non-cycling neuronal cells in *D. melanogaster*. The resulting developmental phenotypes support non-mitotic roles for the complex.
56. Gosling, K. M., Goodnow, C. C., Verma, N. K. & Fahrer, A. M. Defective T-cell function leading to reduced antibody production in a *kleisin*-β mutant mouse. *Immunology* **125**, 208–217 (2008).
57. Gosling, K. M. *et al.* A mutation in a chromosome condensin II subunit, kleisin β, specifically disrupts T cell development. *Proc. Natl Acad. Sci. USA* **104**, 12445–12450 (2007).
58. Guacci, V., Koshland, D. & Strunnikov, A. A direct link between sister chromatid cohesion and chromosome condensation revealed through the analysis of *MCD1* in *S. cerevisiae*. *Cell* **91**, 47–57 (1997).
59. Losada, A., Hirano, M. & Hirano, T. Identification of *Xenopus* SMC protein complexes required for sister chromatid cohesion. *Genes Dev.* **12**, 1986–1997 (1998).
60. Michaelis, C., Ciosk, R. & Nasmyth, K. Cohesins: chromosomal proteins that prevent premature separation of sister chromatids. *Cell* **91**, 35–45 (1997).
61. Klein, F. *et al.* A central role for cohesins in sister chromatid cohesion, formation of axial elements, and recombination during yeast meiosis. *Cell* **98**, 91–103 (1999).
62. Toth, A. *et al.* Functional genomics identifies monopolin: a kinetochore protein required for segregation of homologs during meiosis I. *Cell* **103**, 1155–1168 (2000).
63. Watanabe, Y. & Nurse, P. Cohesin Rec8 is required for reductional chromosome segregation at meiosis. *Nature* **400**, 461–464 (1999).
64. Brar, G. A., Hochwagen, A., Ee, L. S. & Amon, A. The multiple roles of cohesin in meiotic chromosome morphogenesis and pairing. *Mol. Biol. Cell* **20**, 1030–1047 (2009).
65. Hochwagen, A., Tham, W. H., Brar, G. A. & Amon, A. The FK506 binding protein Fpr3 counteracts protein phosphatase 1 to maintain meiotic recombination checkpoint activity. *Cell* **122**, 861–873 (2005).
66. Bannister, L. A., Reinholdt, L. G., Munroe, R. J. & Schimenti, J. C. Positional cloning and characterization of mouse *mei8*, a disrupted allele of the meiotic cohesin *Rec8*. *Genesis* **40**, 184–194 (2004).
67. Martinez-Perez, E. *et al.* Crossovers trigger a remodeling of meiotic chromosome axis composition that is linked to two-step loss of sister chromatid cohesion. *Genes Dev.* **22**, 2886–2901 (2008).
68. Bhatt, A. M. *et al.* The *DIF1* gene of *Arabidopsis* is required for meiotic chromosome segregation and belongs to the *REC8/RAD21* cohesin gene family. *Plant J.* **19**, 463–472 (1999).
69. Colaiacovo, M. P. *et al.* Synaptonemal complex assembly in *C. elegans* is dispensable for loading strand-exchange proteins but critical for proper completion of recombination. *Dev. Cell* **5**, 463–474 (2003).
70. Kleckner, N. Chiasma formation: chromatin/axis interplay and the role(s) of the synaptonemal complex. *Chromosoma* **115**, 175–194 (2006).
71. Severson, A. F., Ling, L., van Zuylen, V. & Meyer, B. J. The axial element protein HTP-3 promotes cohesin loading and meiotic axis assembly in *C. elegans* to implement the meiotic program of chromosome segregation. *Genes Dev.* **23**, 1763–1778 (2009).
This paper showed that multiple cohesin complexes that differ in a single subunit perform specialized functions during *C. elegans* meiosis. Published data suggest that the involvement of multiple cohesins during meiosis may be conserved in many plants and animals.
72. Pasierbek, P. *et al.* A *Caenorhabditis elegans* cohesion protein with functions in meiotic chromosome pairing and disjunction. *Genes Dev.* **15**, 1349–1360 (2001).
73. Goodyer, W. *et al.* HTP-3 links DSB formation with homolog pairing and crossing over during *C. elegans* meiosis. *Dev. Cell* **14**, 263–274 (2008).
74. Pasierbek, P. *et al.* The *Caenorhabditis elegans* SCC-3 homologue is required for meiotic synapsis and for proper chromosome disjunction in mitosis and meiosis. *Exp. Cell Res.* **289**, 245–255 (2003).
75. Golubovskaya, I. N. *et al.* Alleles of *afd1* dissect REC8 functions during meiotic prophase I. *J. Cell Sci.* **119**, 3306–3315 (2006).
76. Xu, H., Beasley, M. D., Warren, W. D., van der Horst, G. T. & McKay, M. J. Absence of mouse REC8 cohesin promotes synapsis of sister chromatids in meiosis. *Dev. Cell* **8**, 949–961 (2005).
77. Hagstrom, K. A., Holmes, V. F., Cozzarelli, N. R. & Meyer, B. J. *C. elegans* condensin promotes mitotic chromosome architecture, centromere organization, and sister chromatid segregation during mitosis and meiosis. *Genes Dev.* **16**, 729–742 (2002).
78. Chan, R. C., Severson, A. F. & Meyer, B. J. Condensin restructures chromosomes in preparation for meiotic divisions. *J. Cell Biol.* **167**, 613–625 (2004).
79. Hartl, T. A., Sweeney, S. J., Knepler, P. J. & Bosco, G. Condensin II resolves chromosomal associations to enable anaphase I segregation in *Drosophila* male meiosis. *PLoS Genet.* **4**, e1000228 (2008).
80. Siddiqui, N. U., Stronghill, P. E., Dengler, R. E., Hasenkampf, C. A. & Riggs, C. D. Mutations in *Arabidopsis* condensin genes disrupt embryogenesis, meristem organization and segregation of homologous chromosomes during meiosis. *Development* **130**, 3283–3295 (2003).
81. Yu, H. G. & Koshland, D. E. Meiotic condensin is required for proper chromosome compaction, SC assembly, and resolution of recombination-dependent chromosome linkages. *J. Cell Biol.* **163**, 937–947 (2003).
82. Yu, H. G. & Koshland, D. Chromosome morphogenesis: condensin-dependent cohesin removal during meiosis. *Cell* **123**, 397–407 (2005).
83. Mets, D. G. & Meyer, B. J. Condensins regulate meiotic DNA break distribution, thus crossover frequency, by controlling chromosome structure. *Cell* **139**, 73–86 (2009).
This paper showed that condensin complexes regulate the number and distribution of DNA DSBs, and thereby COs, during *C. elegans* meiosis. Mutations that disrupt subunits of condensin I and II affect CO number and distribution in different ways, indicating that the two condensin complexes together influence the recombination landscape.
84. Tsai, C. J. *et al.* Meiotic crossover number and distribution are regulated by a dosage compensation protein that resembles a condensin subunit. *Genes Dev.* **22**, 194–211 (2008).
85. Revenkova, E. *et al.* Cohesin SMC1β is required for meiotic chromosome dynamics, sister chromatid cohesion and DNA recombination. *Nature Cell Biol.* **6**, 555–562 (2004).
86. Novak, I. *et al.* Cohesin Smc1β determines meiotic chromatin axis loop organization. *J. Cell Biol.* **180**, 83–90 (2008).
87. Uhlmann, F., Wernic, D., Poupart, M. A., Koonin, E. V. & Nasmyth, K. Cleavage of cohesin by the CD clan protease separin triggers anaphase in yeast. *Cell* **103**, 375–386 (2000).

88. Hauf, S., Waizenegger, I. C. & Peters, J. M. Cohesin cleavage by separase required for anaphase and cytokinesis in human cells. *Science* **293**, 1320–1323 (2001).
89. Bernard, P. *et al.* A screen for cohesion mutants uncovers Ssl3, the fission yeast counterpart of the cohesin loading factor Scc4. *Curr. Biol.* **16**, 875–881 (2006).
90. Ciosk, R. *et al.* Cohesin's binding to chromosomes depends on a separate complex consisting of Scc2 and Scc4 proteins. *Mol. Cell* **5**, 243–254 (2000).
91. Seitan, V. C. *et al.* Metazoan Scc4 homologs link sister chromatid cohesion to cell and axon migration guidance. *PLoS Biol.* **4**, e242 (2006).
92. Watrin, E. *et al.* Human Scc4 is required for cohesin binding to chromatin, sister-chromatid cohesion, and mitotic progression. *Curr. Biol.* **16**, 863–874 (2006).
93. Toth, A. *et al.* Yeast cohesin complex requires a conserved protein, Eco1p(Ctf7), to establish cohesion between sister chromatids during DNA replication. *Genes Dev.* **13**, 320–333 (1999).
94. Takahashi, T. S., Basu, A., Bermudez, V., Hurwitz, J. & Walter, J. C. Cdc7–Drf1 kinase links chromosome cohesion to the initiation of DNA replication in *Xenopus* egg extracts. *Genes Dev.* **22**, 1894–1905 (2008).
95. Ocampo-Hafalla, M. T., Katou, Y., Shirahige, K. & Uhlmann, F. Displacement and re-accumulation of centromeric cohesin during transient pre-anaphase centromere splitting. *Chromosoma* **116**, 531–544 (2007).
96. Gause, M. *et al.* Functional links between *Drosophila* Nipped-B and cohesin in somatic and meiotic cells. *Chromosoma* **117**, 51–66 (2008).
97. Glynn, E. F. *et al.* Genome-wide mapping of the cohesin complex in the yeast *Saccharomyces cerevisiae*. *PLoS Biol.* **2**, e259 (2004).
98. Kogut, I., Wang, J., Guacci, V., Mistry, R. K. & Megee, P. C. The Scc2/Scc4 cohesin loader determines the distribution of cohesin on budding yeast chromosomes. *Genes Dev.* **23**, 2345–2357 (2009).
99. Liu, J. *et al.* Transcriptional dysregulation in *NIPBL* and cohesin mutant human cells. *PLoS Biol.* **7**, e1000119 (2009).
100. Kobayashi, T. & Ganley, A. R. Recombination regulation by transcription-induced cohesin dissociation in rDNA repeats. *Science* **309**, 1581–1584 (2005).
101. Adelfalk, C. *et al.* Cohesin SMC1β protects telomeres in meiocytes. *J. Cell Biol.* **187**, 185–199 (2009).
102. Revenkova, E. & Jessberger, R. Shaping meiotic prophase chromosomes: cohesins and synaptonemal complex proteins. *Chromosoma* **115**, 235–240 (2006).
103. Ono, T. *et al.* Differential contributions of condensin I and condensin II to mitotic chromosome architecture in vertebrate cells. *Cell* **115**, 109–121 (2003).
104. Csankovszki, G. *et al.* Three distinct condensin complexes control *C. elegans* chromosome dynamics. *Curr. Biol.* **19**, 9–19 (2009).
105. Heidinger-Pauli, J. M., Unal, E., Guacci, V. & Koshland, D. The kleisin subunit of cohesin dictates damage-induced cohesion. *Mol. Cell* **31**, 47–56 (2008).
This paper shows that, of many amino acid changes between Scc1 and Rec8, one is largely responsible for the different abilities of Scc1 cohesin and Rec8 cohesin to establish cohesion in response to DNA damage in G2/M phase.
106. Onn, I., Aono, N., Hirano, M. & Hirano, T. Reconstitution and subunit geometry of human condensin complexes. *EMBO J.* **26**, 1024–1034 (2007).
107. Gaszner, M. & Felsenfeld, G. Insulators: exploiting transcriptional and epigenetic mechanisms. *Nature Rev. Genet.* **7**, 703–713 (2006).
108. Zickler, D. & Kleckner, N. Meiotic chromosomes: integrating structure and function. *Annu. Rev. Genet.* **33**, 603–754 (1999).
109. Sakuno, T. & Watanabe, Y. Studies of meiosis disclose distinct roles of cohesion in the core centromere and pericentromeric regions. *Chromosome Res.* **17**, 239–249 (2009).
110. Lengronne, A. *et al.* Establishment of sister chromatid cohesion at the *S. cerevisiae* replication fork. *Mol. Cell* **23**, 787–799 (2006).
111. Ben-Shahar, T. R. *et al.* Eco1-dependent cohesin acetylation during establishment of sister chromatid cohesion. *Science* **321**, 563–566 (2008).
112. Rowland, B. D. *et al.* Building sister chromatid cohesion: Smc3 acetylation counteracts an antiestablishment activity. *Mol. Cell* **33**, 763–774 (2009).
113. Unal, E. *et al.* A molecular determinant for the establishment of sister chromatid cohesion. *Science* **321**, 566–569 (2008).
114. Zhang, J. *et al.* Acetylation of Smc3 by Eco1 is required for S phase sister chromatid cohesion in both human and yeast. *Mol. Cell* **31**, 143–151 (2008).
115. Strom, L. *et al.* Postreplicative formation of cohesion is required for repair and induced by a single DNA break. *Science* **317**, 242–245 (2007).
116. Unal, E., Heidinger-Pauli, J. M. & Koshland, D. DNA double-strand breaks trigger genome-wide sister-chromatid cohesion through Eco1 (Ctf7). *Science* **317**, 245–248 (2007).
117. Alexandru, G., Uhlmann, F., Mechtler, K., Poupart, M. A. & Nasmyth, K. Phosphorylation of the cohesin subunit Scc1 by Polo/Cdc5 kinase regulates sister chromatid separation in yeast. *Cell* **105**, 459–472 (2001).
118. Giet, R. & Glover, D. M. *Drosophila* Aurora B kinase is required for histone H3 phosphorylation and condensin recruitment during chromosome condensation and to organize the central spindle during cytokinesis. *J. Cell Biol.* **152**, 669–682 (2001).
119. Lipp, J. J., Hirota, T., Poser, I. & Peters, J. M. Aurora B controls the association of condensin I but not condensin II with mitotic chromosomes. *J. Cell Sci.* **120**, 1245–1255 (2007).
120. Takemoto, A. *et al.* Analysis of the role of Aurora B on the chromosomal targeting of condensin I. *Nucleic Acids Res.* **35**, 2403–2412 (2007).
121. Takemoto, A., Kimura, K., Yanagisawa, J., Yokoyama, S. & Hanaoka, F. Negative regulation of condensin I by CK2-mediated phosphorylation. *EMBO J.* **25**, 5339–5348 (2006).
122. St-Pierre, J. *et al.* Polo kinase regulates mitotic chromosome condensation by hyperactivation of condensin DNA supercoiling activity. *Mol. Cell* **34**, 416–426 (2009).
123. Miller, L. M., Plenefisch, J. D., Casson, L. P. & Meyer, B. J. *xol-1*: a gene that controls the male modes of both sex determination and X chromosome dosage compensation in *C. elegans*. *Cell* **55**, 167–183 (1988).
124. Rhind, N. R., Miller, L. M., Kopczynski, J. B. & Meyer, B. J. *xol-1* acts as an early switch in the *C. elegans* male/hermaphrodite decision. *Cell* **80**, 71–82 (1995).
125. Dawes, H. E. *et al.* Dosage compensation proteins targeted to X chromosomes by a determinant of hermaphrodite fate. *Science* **284**, 1800–1804 (1999).
126. Chu, D. S. *et al.* A molecular link between gene-specific and chromosome-wide transcriptional repression. *Genes Dev.* **16**, 796–805 (2002).

Acknowledgements
We apologize to researchers whose work we were unable to cite owing to space constraints. We thank R. Holmes, F. Tan and L. Wahba for comments on the manuscript, A. Michel and B. Pferdehirt for images in figure 1, and J. Gunther for illustrations. A.J.W. has been funded by a Sir Henry Welcome Post-Doctoral Research Fellowship and B.J.M. by the US National Institutes of Health. B.J.M. is an Investigator of the Howard Hughes Medical Institute.

Competing interests statement
The authors declare no competing financial interests.

DATABASES
Entrez Gene: http://www.ncbi.nlm.nih.gov/gene
her-1 | *sdc-2* | *SMC1* | *SMC3* | *xol-1*
FlyBase: http://flybase.org
Nipped-B
UniProtKB: http://www.uniprot.org
Cdc5 | Chk1 | CTCF | DPY-27 | DPY-30 | MIX-1 | Scc2 | SDC-1 | SDC-3 | SMC-4

FURTHER INFORMATION
Barbara J. Meyer's homepage:
http://mcb.berkeley.edu/labs/meyer
WormBase: http://www.wormbase.org

ALL LINKS ARE ACTIVE IN THE ONLINE PDF