Current Genetics (2019) 65:407–415
https://doi.org/10.1007/s00294-018-0899-4

MINI-REVIEW

# Condensin action and compaction

**Matthew Robert Paul**[1,2] · **Andreas Hochwagen**[1] · **Sevinç Ercan**[1,2]

Received: 12 October 2018 / Revised: 18 October 2018 / Accepted: 20 October 2018 / Published online: 25 October 2018


**Abstract**
Condensin is a multi-subunit protein complex that belongs to the family of structural maintenance of chromosomes (SMC) complexes. Condensins regulate chromosome structure in a wide range of processes including chromosome segregation, gene regulation, DNA repair and recombination. Recent research defined the structural features and molecular activities of condensins, but it is unclear how these activities are connected to the multitude of phenotypes and functions attributed to condensins. In this review, we briefly discuss the different molecular mechanisms by which condensins may regulate global chromosome compaction, organization of topologically associated domains, clustering of specific loci such as tRNA genes, rDNA segregation, and gene regulation.

**Keywords** Genome organization · Condensin · Chromosome interactions · gene expression · TADs · SMCcomplexes · rDNA · tRNA · Clustering · Chromosome segregation · Transcription

## Chromosome remodeling by condensin

The major molecular activity of condensins is forming chromosomal loops through their conserved SMC ring structure (Cuylen et al. 2011; van Ruiten and Rowland 2018). SMC complexes are thought to form such loops by loop extrusion, a process in which DNA is pushed through the SMC ring in an ATPase dependent manner (Nasmyth 2001; Goloborodko et al. 2016a). Loop extrusion by condensin is well supported by in vitro experiments using DNA curtains (Terakawa et al. 2017) and by single-molecule imaging (Ganji et al. 2018). In vivo evidence of loop extrusion stems mostly from the *Bacillus subtilis* SMC complex, which functions to juxtapose the two arms of the bacterial chromosome. By measuring the speed of this juxtaposition, the speed of *B. subtilis* SMC complex movement along the chromosome was estimated to be ~0.8 kb/s (Wang et al. 2017b). Yeast condensin extruded DNA at a similar rate in vitro, with speeds up to 1.5 kb/s depending on the concentration of ATP (Terakawa et al. 2017; Ganji et al. 2018). Accordingly, mutations that affect the ATPase activity changed the speed of the *B. subtilis* SMC complex (Wang et al. 2018b). In addition, the speed of extrusion was affected by transcription in *B. subtilis* (Wang et al. 2017b), suggesting that obstacles on the DNA, including chromatin in eukaryotes, may regulate condensin processivity.

## Condensins regulate chromosome compaction for cell division

The major function of condensins in all eukaryotes is their essential role in chromosome assembly and segregation during mitosis and meiosis (Chan et al. 2004; Cuylen and Haering 2011; Houlard et al. 2015; Kinoshita and Hirano 2017; Kakui and Uhlmann 2018). In preparation for cell division, chromosomes assume a highly compacted structure, characterized by extensive looping of the chromatin fiber. Following condensin inactivation, loop formation and compaction are severely disrupted as indicated by global mapping of chromosomal interactions within mitotic chromosomes (Kakui et al. 2017; Schalbetter et al. 2017; Gibcus et al. 2018). Loop extrusion is likely one of the central drivers

Communicated by M. Kupiec.

✉ Andreas Hochwagen
andi@nyu.edu

✉ Sevinç Ercan
se71@nyu.edu

[1] Department of Biology, New York University, New York, NY 10003, USA

[2] Center for Genomics and Systems Biology, New York University, New York, NY 10003, USA

of chromosome compaction, and models based on loop extrusion can explain the formation of chromosomal loops in mitotic chromosomes (Fig. 1ai, ii) (Goloborodko et al. 2016a, b; Gibcus et al. 2018; Kakui and Uhlmann 2018). Interestingly, the range of loops mediated by condensin differs among organisms (Kakui and Uhlmann 2018). Unlike yeast, where there is a single condensin, metazoans contain two condensin types, named condensin I and II (Hirano 2016). Specific knockout experiments and imaging of the two condensin complexes suggest that condensin II mediates longer loops and sets up the axis of mitotic chromosomes, while condensin I mediates shorter loops thickening the

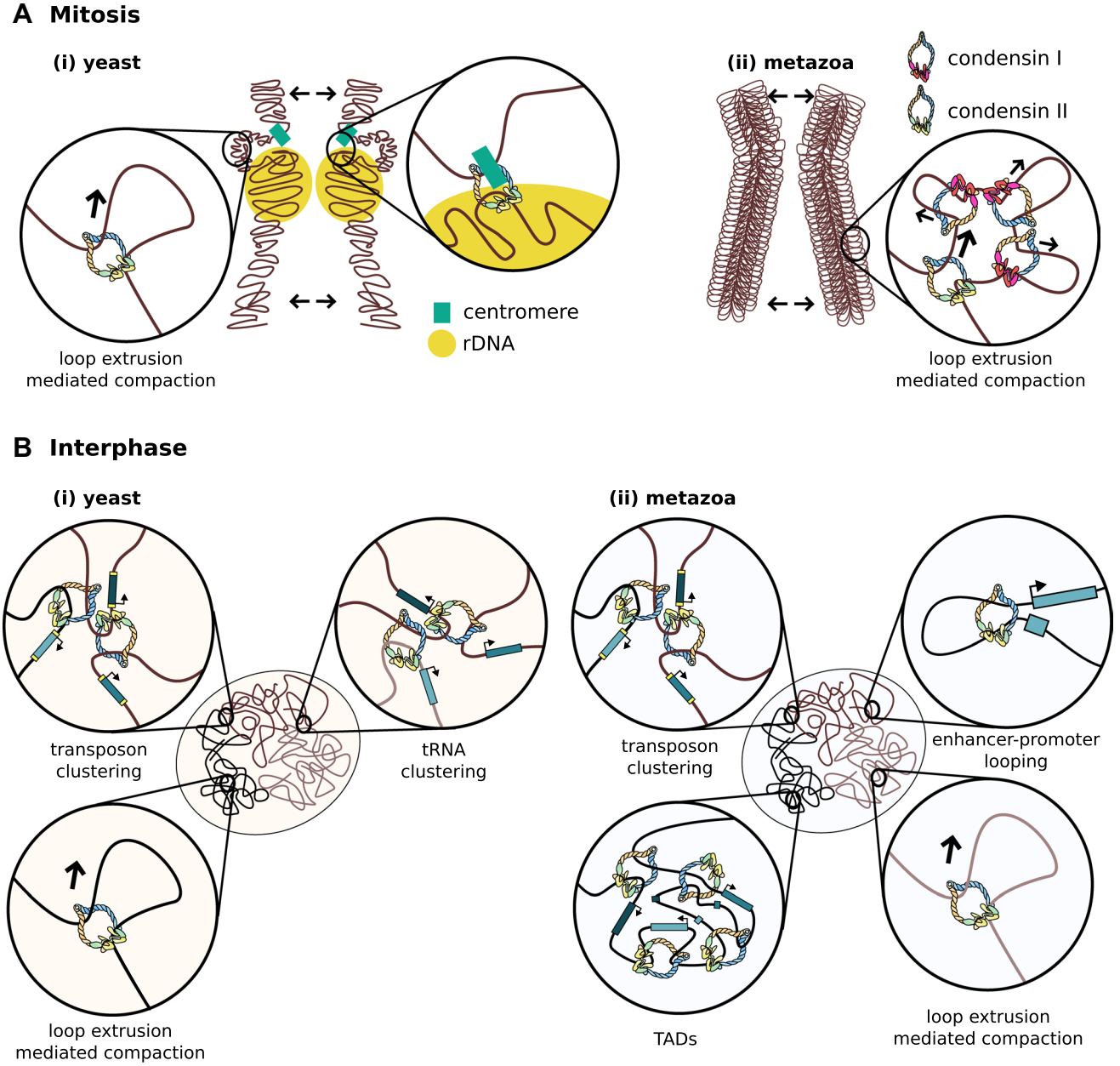


**Fig. 1** Condensin-mediated genome organization: **a** Mitotic structure of chromosomes in yeast (i) and metazoans (ii). (i) In yeast, condensin compacts the rDNA and tethers the rDNA to the centromere. The centromere-proximal side of the rDNA is enriched for condensin, which compacts chromosomes through loop extrusion. (ii) In metazoans, there are two condensin complexes, which function on different scales (condensin I: shorter loops, condensin II: longer loops). Together, condensin I and II compact chromosomes through loop extrusion, forming nested loop structures. **b** Interphase structure of chromosomes in yeast (i) and metazoans (ii). (i) In yeast, condensin compacts chromosomes through loop extrusion and aids clustering of tRNAs and transposons by promoting long-range interactions. (ii) In metazoans, condensin compacts chromosomes through loop extrusion, clusters transposons and enhancer–promoter pairs by promoting long-range interactions, and aids the formation of TADs

mitotic chromosomes (Fig. 1aii) (Hirota et al. 2004; Green et al. 2012; Kinoshita and Hirano 2017; Walther et al. 2018).

## The role of condensins in interphase genome organization

In addition to compacting the chromosomes in preparation for segregation, condensin function is required for interphase structures (Albritton and Ercan 2018; Yuen and Gerton 2018). In *Drosophila melanogaster*, condensin II promotes axial compaction of chromosomes to form chromosomal territories (Bauer et al. 2012; Smith et al. 2013; George et al. 2014; Rosin et al. 2018). In *Caenorhabditis elegans*, an X-chromosome specific condensin (condensin DC) is responsible for a ~ 40% reduction in the volume of the X chromosomes compared to the autosomes (Lau et al. 2014). In this context, condensin DC mediates shorter scale chromosomal interactions as well as specific long-range interactions on the X (Crane et al. 2015). Condensin depletion also caused decompaction of interphase nuclei in mouse embryonic stem cells (Fig. 1bi, ii) (Fazzio and Panning 2010).

Interphase organization of the eukaryotic nucleus involves chromatin fibers that fold into nested interaction domains termed topologically associated domains (TADs) (Sexton et al. 2012; Rao et al. 2014). It is hypothesized that TADs function to restrict the search space for enhancer–promoter interactions, allowing coherent and correct expression of genes (Lupianez et al. 2015). Establishment of TADs has primarily been linked to the function of cohesin, another SMC complex, but condensin has recently emerged as additional TAD regulator (Yuen and Gerton 2018). Insulator proteins, such as CTCF, block SMC complex movement to delimit TAD boundaries (Fudenberg et al. 2016). Condensins colocalize with cohesin at the CTCF sites found at the strongest TAD boundaries in mouse (Van Bortle et al. 2014), and were shown to regulate TAD organization in *D. melanogaster* and *C. elegans* (Fig. 1bii) (Van Bortle et al. 2014; Crane et al. 2015; Li et al. 2015a). However, in differentiated mouse hepatocytes condensin II depletion did not affect TADs, suggesting that condensins may be involved in establishment rather than maintenance of genome organization during interphase (Abdennur et al. 2018). Developing an understanding of TAD organization and the role of condensin in this process is an important next step in the field.

## The role of condensins in regulating rDNA structure and organization

In addition to general roles in chromosome organization, condensins also play important roles in the organization of specific genomic elements. One of the best-understood examples in this context is the function of condensin in regulating compaction and segregation of the ribosomal DNA (rDNA). The rDNA is one of the most difficult regions of the genome to segregate during cell division (Freeman et al. 2000; D'Ambrosio et al. 2008a). The segregation problems are likely due to the high level of repetition, active transcription, and late replication (Bhalla et al. 2002; D'Ambrosio et al. 2008a). In *S. cerevisiae*, where most of these analyses were conducted, the rDNA is segregated by gradual extension and unzipping of the rDNA repeats followed by axial compaction (Machín et al. 2005; D'Ambrosio et al. 2008a). This multi-step process is essential, as triggering premature rDNA compaction delays segregation (de los Santos-Velázquez et al. 2017).

In addition to helping compact the rDNA array, condensin also mediates a specific long-range interaction between the rDNA and the centromere of the rDNA-carrying chromosome (Paul et al. 2018). The centromere-rDNA interaction peaks during anaphase, matching the timing of segregation (Lazar-Stefanita et al. 2017). rDNA unzipping during segregation initiates on the centromere-proximal side (Machín et al. 2005), where condensin binding is enriched (Paul et al. 2018), raising the possibility that condensin-mediated proximity of the rDNA to the centromere may play a role in rDNA segregation (Fig. 1ai). This mechanism may involve a direct centromere tether to the rDNA that helps facilitate segregation. Alternatively, the enrichment of condensin between the centromere and the rDNA may either allow more efficient decoupling of sister rDNA arrays or may help protect the DNA between the rDNA and centromere from the high tension generated by the pulling of the spindle against the entangled rDNA.

In *S. cerevisiae*, condensin is also essential for regulating the rDNA upon nutrient starvation (Tsang et al. 2007a; Xue and Acar 2018). rDNA compaction in response to both starvation and segregation, is accompanied by the exodus of RNA polymerase I from the nucleolus (Tsang et al. 2003; Machín et al. 2006). Thus, active transcription at the rDNA appears to have an antagonistic relationship with condensin, which is opposite to what is found in the rest of the genome (Robellet et al. 2017). There is a modest increase in interaction between the rDNA and the centromere proximal side of the rDNA during starvation, indicating that chromosome segregation and quiescence trigger a similar pattern of condensin-dependent compaction (Swygert et al. 2018). However, the mechanism of condensin regulation likely differs between the two processes. Condensin recruitment during segregation requires the replication fork barrier protein Fob1 (Johzuka et al. 2006) and inactivation of rDNA transcription by the cell-cycle phosphatase Cdc14 (D'Amours et al. 2004; Wang et al. 2006; Machín et al. 2006; Dulev et al. 2008; Clemente-Blanco et al. 2009; Matos-Perdomo and Machín 2018), whereas recruitment during starvation is initiated by

Rpd3-dependent histone deacetylation (Tsang et al. 2007a). Condensin binding to the rDNA helps maintain rDNA stability during starvation stress (Tsang et al. 2007b; Tsang and Zheng 2009), possibly in part by helping establish a position-dependent structure within the rDNA, that limits activity of RNA polymerase II to a few border repeats and allows protection of the silent majority of the rDNA (Wang et al. 2016).

rDNA is fundamental to cell physiology, and the few available studies in other organisms suggest a conservation for condensin function in rDNA regulation. In human cells, condensin knockdown resulted in increased rDNA expression, suggesting the antagonistic relationship between rDNA transcription and condensin may be conserved (Huang et al. 2013). In chicken cells, condensin I is enriched at the rDNA, and depletion of condensin I results in rDNA decompaction (Zhang et al. 2016). During meiosis, condensin contributes to rDNA compaction in *A. thaliana* and prevents crossovers at the rDNA by suppressing programmed double strand breaks in *S. cerevisiae* (Li et al. 2014; Smith et al. 2014). Similarly, the human rDNA is unstable in the absence of condensin (Samoshkin et al. 2012).

## Condensin-mediated clustering of specific genomic loci including tRNA genes

Condensin also drives specific interactions between distant loci. Condensin is enriched at the tRNA genes in many organisms, including *S. cerevisiae, S. pombe, D. melanogaster, C. elegans*, mouse and human (D'Ambrosio et al. 2008b; Kranz et al. 2013; Van Bortle et al. 2014; Iwasaki et al. 2015; Yuen et al. 2017). In *S. pombe*, the TATA-binding protein TBP recruits condensin to tRNA genes, while in *S. cerevisiae*, the TFIIIC complex was shown to be capable of recruiting condensin (D'Ambrosio et al. 2008b; Iwasaki et al. 2015). Furthermore, condensin binds to RNA polymerase III specific subunits including TFIIIB, TFIIIC, RPC82, RPC25 (Haeusler et al. 2008; Iwasaki et al. 2010). In yeasts, condensin is required to cluster tRNA genes (Haeusler et al. 2008; Iwasaki et al. 2010; Paul et al. 2018). Interestingly, in *S. cerevisiae* this clustering is specific for a family of tRNA genes, suggesting a possible regulatory function (Paul et al. 2018). It is important to note that the tRNA genes clustered by condensins are located on different chromosomes. Thus, a model of loop extrusion is insufficient to explain these *trans* interactions. Supporting the ability of condensins to make *trans* connections (Fig. 1Bi), *S. cerevisiae* condensin was shown to be able to hold two separate DNA pieces together in vitro (Terakawa et al. 2017), and interactions between different condensin molecules were needed in a computational model for the formation of the mitotic chromosome (Sakai et al. 2018).

It is possible that condensin-mediated clustering establishes structures much like 'transcription factories', in which co-regulated genes are clustered together to allow enrichment of regulators in one place (Branco and Pombo 2006; Du and Bai 2017). In *S. pombe*, reduction in tRNA gene clustering resulted in increased transcription (Iwasaki et al. 2010). Given the fact that RNA polymerase III recruits condensin, this would suggest that there is some form of negative feedback in the system. In *S. cerevisiae*, tRNA genes that clustered in a condensin dependent manner were bound by RNA polymerase III at a slightly higher level, suggesting a positive effect for condensin in their transcription (Paul et al. 2018). Condensin effects on clustering are not limited to interactions among tRNA genes. tRNA genes also cluster with other genomic features, including the rDNA in *S. cerevisiae*, and centromeres and cell-cycle regulated genes in *S. pombe* (Haeusler et al. 2008; Kim et al. 2016; Paul et al. 2018). Moreover, condensins also drive the association of other dispersed genomic loci. One example is centromere clustering, which is required for the repression of retrotransposons in *S. pombe* (Fig. 1bi) (Tanaka et al. 2012). Indeed, this function may be conserved in humans, *Arabidopsis thaliana* and *D. melanogaster*, where condensin was required to repress transposon expression (Fig. 1bii) (Wang et al. 2011, 2017a; Schuster et al. 2013). Together, these observations imply that condensin not only acts by loop-extrusion but also provides an important mechanism to selectively regulate chromatin interactions in *trans*.

## Condensin function in gene regulation

A clear paradigm of condensin-mediated gene regulation is the *C. elegans* condensin DC complex, which represses both X chromosomes by a factor of two in XX hermaphrodites to equalize X chromosomal transcript levels to that of XO males. The mechanisms by which condensin DC regulates transcription has been reviewed recently (Albritton and Ercan 2018). Briefly, condensin DC specifically binds to promoters in a gene-activity dependent manner and, in turn, reduces RNA polymerase II binding to promoters, resulting in transcriptional repression. Condensin DC shares four subunits with canonical condensin I and differs from it by a single SMC4 subunit that duplicated and diverged in *Caenorhabditis* (Csankovszki et al. 2009). Evolution of SMC subunits for new functions is also evident in mammals, where an SMC variant named SMCHD1, which makes homodimers like prokaryotic condensins (Brideau et al. 2015), is involved in X inactivation by regulating chromosomal interactions on the inactivated X (Nozawa et al. 2013; Chen et al. 2015; Wang et al. 2018a; Jansz et al. 2018) and in Hox clusters (Jansz et al. 2018). A recent study identified an SMC like protein, SMCL1 that regulates condensin binding in *C.*

*elegans* (Chao et al. 2017). Therefore, future work should focus on the evolution of SMC variants in regulating canonical SMC complex functions.

Whether and how canonical condensins directly or indirectly regulate transcription remains unclear. Two recent analyses in *S. cerevisiae* showed that yeast condensin does not directly regulate transcription (Paul et al. 2018; Hocquet et al. 2018). Similarly, condensin II depletion in postmitotic mouse hepatocyte cells and condensin II mutations in T cell leukemia did not affect mRNA expression in mouse (Woodward et al. 2016; Abdennur et al. 2018). In yeast, chronic perturbation of condensin resulted in increased mRNA levels (Swygert et al. 2018; Paul et al. 2018). Some of these effects may be indirect, because in *S. pombe* and *S. cerevisiae*, increased mRNA levels upon condensin depletion were linked to chromosome segregation defects of the rDNA. These defects were linked to missegregation of the RNA exosome, leading to mRNA increase in the daughter cells (Hocquet et al. 2018). Therefore, canonical condensin function in gene regulation may be coupled to its role in cell division, such that condensin-mediated assembly of mitotic chromosome structure may regulate establishment of genome organization and gene expression patterns during interphase.

## Condensin action on chromosomes and transcription

Condensin binding is enriched at the promoters and gene regulatory regions in *C. elegans* (Kranz et al. 2013), *D. melanogaster* (Wallace et al. 2015), chicken (Kim et al. 2013), and mouse (Yuen et al. 2017), and condensin knockdown and mutations have been shown to affect gene expression in several of these organisms (Longworth et al. 2012; Kranz et al. 2013; Lau and Csankovszki 2015; Schuster et al. 2015; Li et al. 2015b; Swygert et al. 2018). However, the link between widespread enrichment of canonical condensins at gene regulatory sites and transcription remains unclear. Similar to cohesin, condensin was implicated in specific long-range interaction between several enhancers and promoters in human cell lines to promote gene expression (Fig. 1bii) (Dowen et al. 2013; Li et al. 2015b). Interestingly, some of these enhancers use phase separation to mediate gene regulation (Sabari et al. 2018). One of the first nuclear bodies that was shown to undergo phase-separation was the nucleolus, a focus of condensin enrichment (Feric et al. 2016; Sawyer et al. 2018). It is conceivable that condensin binding affects establishment of liquid phase dynamics of the nucleolus and enhancer–promoter interactions.

A highly specific function of condensins in regulating chromosomal interactions for gene regulation occurs during transvection in *D. melanogaster*. Here, sister chromatids remain paired during interphase, allowing enhancers to act in *trans* to regulate promoters (Mellert and Truman 2012). Condensin antagonizes transvection, presumably by creating discrete chromosomes through loop extrusion as in mitosis (Hartl et al. 2008; Smith et al. 2013). A similar observation was made in mouse neural stem cells, where condensin II antagonizes pericentric heterochromatin clustering at chromocenters (Nishide and Hirano 2014). The involvement of condensin in both transcription activation through promoter-enhancer interactions and repression through antagonizing transvection suggests that the activity of condensins may result in different outcomes depending on the mechanism of gene regulation.

In addition to regulating chromosomal interactions, the action of condensin motors, with a ~ 50 nm ring sliding along the chromatin fiber, may create conflict with large transcription complexes (Terakawa et al. 2017). During mitosis, when condensin activity is at its highest level, transcribing RNA polymerase II complexes are removed from chromatin (Martínez-Balbás et al. 1995; Segil et al. 1996; Gottesfeld and Forbes 1997; Ginno et al. 2018), and mitotic bookmarking requires dissociation of condensin from specific loci (Xing et al. 2005, 2008). In addition to condensin ring sliding, introduction of positive supercoils to mitotic DNA in the presence of topoisomerase II (Hirano et al. 1997; Hagstrom et al. 2002; Stray and Lindsley 2003) or reannealing of single stranded DNA may help condensins repress transcription of mitotic chromosomes (Sutani et al. 2015). In *S. pombe*, inhibition of transcription partly suppressed condensin mutant phenotypes in cell division (Sutani et al. 2015), suggesting that condensin-mediated transcriptional silencing of mitotic chromosomes may be important for chromosome segregation.

## Indirect effects of condensins on gene regulation

Beyond condensin's direct action on DNA, condensin may regulate transcription through histone modifications. In *D. melanogaster*, the condensin II subunit Barren interacts with polycomb proteins to repress homeotic gene expression (Lupo et al. 2001). Likewise in *C. elegans*, condensin DC interacts with a H4K20me2 demethylase, DPY-21 (Brejc et al. 2017). The demethylation product is H4K20me1, which is enriched on the X chromosome and contributes to dosage compensation (Wells et al. 2012; Vielle et al. 2012; Kramer et al. 2015; Bian et al. 2017). In *A. thaliana* condensin meditates silencing of specific transposon families in conjunction with CG methylation by MET1, CHG methylation by CMT3, the chromatin remodeler DDM1 and H3K27 monomethylation (Wang et al. 2017a). In *D. melanogaster*, retrotransposon expression is blocked by condensin II

mediated regulation of H3K9me3 localization (Schuster et al. 2013). Thus, it is possible that condensin also serves as a binding platform to recruit additional regulatory activities for controlling gene expression.

Finally, condensin II was reported to bind LINE-1 RNAs with Gamma-Interferon Activated Inhibitor of Translation (GAIT) in human cells (Ward et al. 2017). Together these protein complexes repressed translation of LINE-1 RNA by stopping the formation of the translation initiation complex. Additional examples of condensin interaction with RNA have yet to be found, but condensin has high affinity for RNAs in vitro (Akai et al. 2011).

## Summary: condensins are integrated into fundamental chromosomal functions

Condensins were identified, because they drive the compaction of chromosome into discrete bodies that are easy to segregate (Hirano et al. 1986; Saka et al. 1994). In the absence of condensin complexes, cells fail to segregate chromosomes faithfully and daughter cells die. As a result, condensins are essential for proper growth and division in all domains of life (Hirano 2016). How then do hypomorphic mutations in condensins trigger tissue-specific problems in cell divisions leading to T-cell lymphoma or microcephaly (Martin et al. 2016; Woodward et al. 2016)? It is possible that the myriad of additional condensin functions that link cell division to cell physiology (e.g., rDNA, RNA exosome segregation, regulation of TADs or tRNA clustering) are in play. Therefore, future insights into interaction of condensins with basic nuclear processes will be important to understand condensin function and phenotypes in disease.

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