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Review

How Chromatin Motor Complexes Influence the Nuclear Architecture: A Review of Chromatin Organization, Cohesins, and Condensins with a Focus on *C. elegans*

Bahaar Chawla and Györgyi Csankovszki *

Department of Molecular, Cellular, and Developmental Biology, University of Michigan, Ann Arbor, MI 48109-1085, USA; bchawla@umich.edu

* Correspondence: gyorgyi@umich.edu; Tel.: +1-(734)-764-3412

Abstract: Chromatin is the complex of DNA and associated proteins found in the nuclei of living organisms. How it is organized is a major research field as it has implications for replication, repair, and gene expression. This review summarizes the current state of the chromatin organization field, with a special focus on chromatin motor complexes cohesin and condensin. Containing the highly conserved SMC proteins, these complexes are responsible for organizing chromatin during cell division. Additionally, research has demonstrated that condensin and cohesin also have important functions during interphase to shape the organization of chromatin and regulate expression of genes. Using the model organism *C. elegans*, the authors review the current knowledge of how these complexes perform such diverse roles and what open questions still exist in the field.

Keywords: chromatin architecture; SMC proteins; condensin; cohesin; TADs; *C. elegans*; dosage compensation

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1. Introduction: Chromatin Organization

The word chromatin comes from the Greek word for color, *khroma*. In the late 1880s, Walter Flemming used this term to describe the dark stained material found in the cell preparations he treated with basophilic dyes [1]. Chromatin is now defined as the complex of DNA and associated proteins found in the nuclei of living organisms. The most discrete unit of eukaryotic chromatin is a nucleosome [2]. Discovered in the 1970s, nucleosomes are structures made up of an octamer of histone proteins and approximately 160 base pairs of DNA wrapped around the octamer, like thread on a spool [3,4]. As the cell is preparing to undergo mitosis, these nucleosomes are tightly condensed until they become the stereotypical chromosomes that can be seen under a microscope. Once cell division is completed, the chromosomes lose this degree of compaction [5].

However, that does not mean that interphase nuclei have no structure or organization. Instead, we now understand that how the chromatin is organized has a major impact on gene expression, tissue specification, and cell homeostasis [6–9]. In fact, long-range communication is known to be essential for gene expression, where a necessary enhancer may be many kilobases away from the promoter and must be brought in contact with the RNA transcription machinery for transcription to proceed [10,11]. One way in which this can be accomplished is through the recruitment of enhancer-binding proteins, such as CCAAT/the Enhancer-Binding Protein Family. Members of this family use their highly conserved basic-leucine zipper domain to both bind DNA and dimerize with other members of the same family or even other transcription factors to bring segments of DNA together by bending the DNA strands physically [12]. These chromatin-organizing events are often transient [13]. Some transcription factors, like those in the WNT signaling family are sequestered in the cytoplasm until circumstances are reached that promote them to

translocate into the nucleus [14]. Therefore, transcription factors and enhancer-binding proteins alone are not the sole drivers of chromatin organization [15].

Instead, there are specific orders of chromatin organization, each accomplished through a variety of drivers. At the lowest level, the positioning of nucleosomes is specific. Nucleosomes are unlikely to be present at transcriptional start sites of actively transcribed genes, but instead, they are found in well-characterized patterns along the rest of the gene body [16]. The next level of organization is the clustering of nucleosomes. Known as "clutches", these are defined as a group of more than three nucleosomes that are distinctly separated from other groups of nucleosomes by a distance more than 20 nm [17,18]. Clutches are often of variable number and density, the latter correlated with cell potency [19]. In somatic cells, clutches tend to have more nucleosomes that are packed in tighter, resulting in higher density. This contrasts with pluripotent cells, where the clutches are smaller and less dense, resulting in more open chromatin [17]. Open chromatin, or euchromatin, is also defined as accessible DNA, where the histone tails of the nucleosomes are modified to prevent tight packaging. This contrasts with heterochromatin, or inactive chromatin, where the nucleosomes can be packed very tightly, facilitated by different post-translational modifications on the histone tails [20].

The next level of chromatin organization is the formation of topologically associated domains, TADs. TADs are higher-order structures that are caused by the increased interaction of DNA within a genomic region with itself compared to interactions with DNA in a different genomic region [21,22]. Genes within a TAD are generally of the same transcriptional state, resulting in enrichment of histone modifications reflecting that state in the TAD [23,24]. TADs have a well-defined size, with the median in mouse cells at 880 kb and similar sizes in non-mammalian cells [21]. TADs are thought to promote gene expression through the close-range organization of enhancers and promoters while also insulating these from other DNA sequences [25]. This has been demonstrated through the removal of a TAD boundary, where the lack of a boundary resulted in new promoter–enhancer interactions and misregulated gene expression [26–28]. TAD boundaries are also very stereotypical and surprisingly well conserved between species [29,30]. However, plants have been shown to not utilize TADs as a method of genome organization [31]. In fact, even in species that do utilize TADs, it has been demonstrated that a large-scale disruption of TADs by depleting the key proteins responsible results in little disruption of gene expression. These results demonstrate that TADs are not the primary way to regulate gene expression, making the goal of understanding the link between chromatin organization and gene regulation still a work in progress [32,33].

The next order of chromatin organization is controversial. Initial studies suggested that chromatin at this level is separated into two compartments, A and B. The A compartment is made up of active chromatin, while the B compartment is made up of inactive chromatin [34,35]. DNA is classified into these compartments based on calculating principal eigenvectors of the frequent contacts in a Hi-C map [36,37]. However, recent work in human lymphoblastoid cells argues that the compartments are much smaller than what was previously defined. The newer smaller size puts compartments at the same resolution as TADs or even smaller, but unlike TADs, their boundaries do not line up with the same protein-enriched loops [38].

The final and highest order of chromatin are chromosome territories. Each chromosome is found in a discrete region of nucleus, and the only instances of overlapping between chromosomes is at the boundaries of their territories [39,40]. Generally, these territories are spherical, as in many mammalian and Arabidopsis cells [41,42]. How these chromosome territories are positioned in the nucleus has been found to be non-random, with euchromatin-rich chromosomes more central and heterochromatin-heavy chromosomes located at the nuclear periphery [43,44]. This organization results in a very complex nuclear architecture, one that is still being dissected to understand the nuances and implications.

This review will focus on chromatin organization and its impact on gene expression. While the focus of the review is condensins in *Caenorhabditis elegans*, this review will

also summarize the literature on cohesins and the role of both complexes in chromatin organization in *C. elegans* as well as other organisms to provide broader context.

2. Structural Maintenance of Chromosome Proteins Are the Backbone of Chromatin Motor Complexes

Structural Maintenance of Chromosome (SMC) proteins are a family of highly conserved proteins found from bacteria to eukaryotes [45]. SMC proteins share a characteristic tertiary structure that allows them to accomplish their various functions [46–48]. Each SMC protein has two globular domains at each terminus that are separated by an alpha-helical region, then a "hinge", and another alpha helix. The SMC proteins fold on their hinges, and the two alpha helices come together as coiled-coil (Figure 1). The coiled-coil brings the two globular domains in contact with each other, where they make up the ATPase "head" [49]. The ATPase is a key functional domain, as studies have shown that preventing ATP hydrolysis will also abolish loop extrusion and other functions of the SMC proteins [46,47].

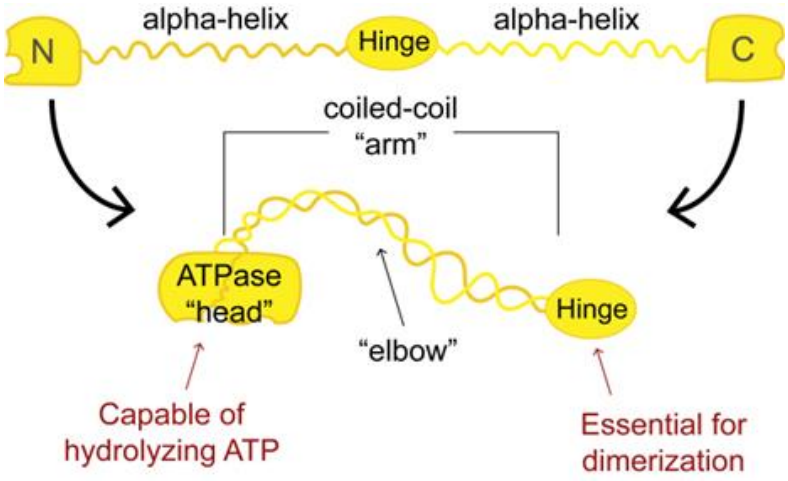

Figure 1. SMC protein folding. An SMC protein is shown at the top with globular N and C terminal domains that are separated by a pair of alpha-helices on either side of a "hinge" domain. Once the hinge folds on itself, the two alpha-helices make up a coiled-coil, which allows for the N and C terminal domains to interact as the ATPase "head". The coiled-coil is sometimes referred to as an "arm" with an "elbow", where flexible bends can occur.

In eukaryotes, there are generally six SMC proteins, named SMC1-6 [50]. These are found in three chromatin motor complexes, with differing functions [50]. SMC-1 and SMC-3 are the SMC protein pair found in cohesin [49]. SMC-5 and SMC-6 are found with a few other proteins in the SMC-5/6 complex, which functions in double-stranded break repair, restarting a stalled replication fork, and maintaining telomeres [51]. The final pair, SMC-2 (known as MIX-1 in *C. elegans*) and SMC-4 are found with three other proteins in complexes known as condensins [50,52]. All SMC proteins function in pairs, as their ATPase head domains require dimerization [46,53]. This dimerization is carried out through specific residues found in the hinge domain. Each hinge domain will interact with the hinge domain of the partnering SMC protein [49,54]. All three SMC protein-containing chromatin motor complexes can loop-extrude DNA. However, they perform very different functions from each other, not all of which contribute to chromatin architecture [45,55].

Along with the SMC proteins, another protein found in chromatin motor complexes is the kleisin. Kleisin comes from the Greek word for closure, *kleisimo* [56]. Kleisins are a superfamily of proteins, but all members are generally known to be SMC partners. There are three eukaryotic families and a single bacterial family. Despite the wide variety in these families, the main motifs that allow the kleisin to bind an SMC head at each terminus are well conserved [57].

The two chromatin motor complexes capable of modifying chromatin architecture, cohesin and condensin, comprise a pair of SMC proteins and a kleisin, along with different regulatory subunits. Cohesin resembles a "ring", through which DNA is loop-extruded (Figure 2A). In *C. elegans*, this ring is made up of SMC-1; SMC-3; the kleisin subunit SCC-1 (sometimes referred to as COH-2); and a HEAT-repeat domain containing regulatory protein, SCC-3 [58]. There are homologues for all cohesin subunits found throughout eukaryotic organisms (see Table 1), with some eukaryotes containing multiple homologues of SCC-1 and SCC-3 [59–61]. These homologues allow for differential regulation and loading of cohesin complexes, which is especially important given the many roles cohesin is responsible for (discussed later in Section 3).

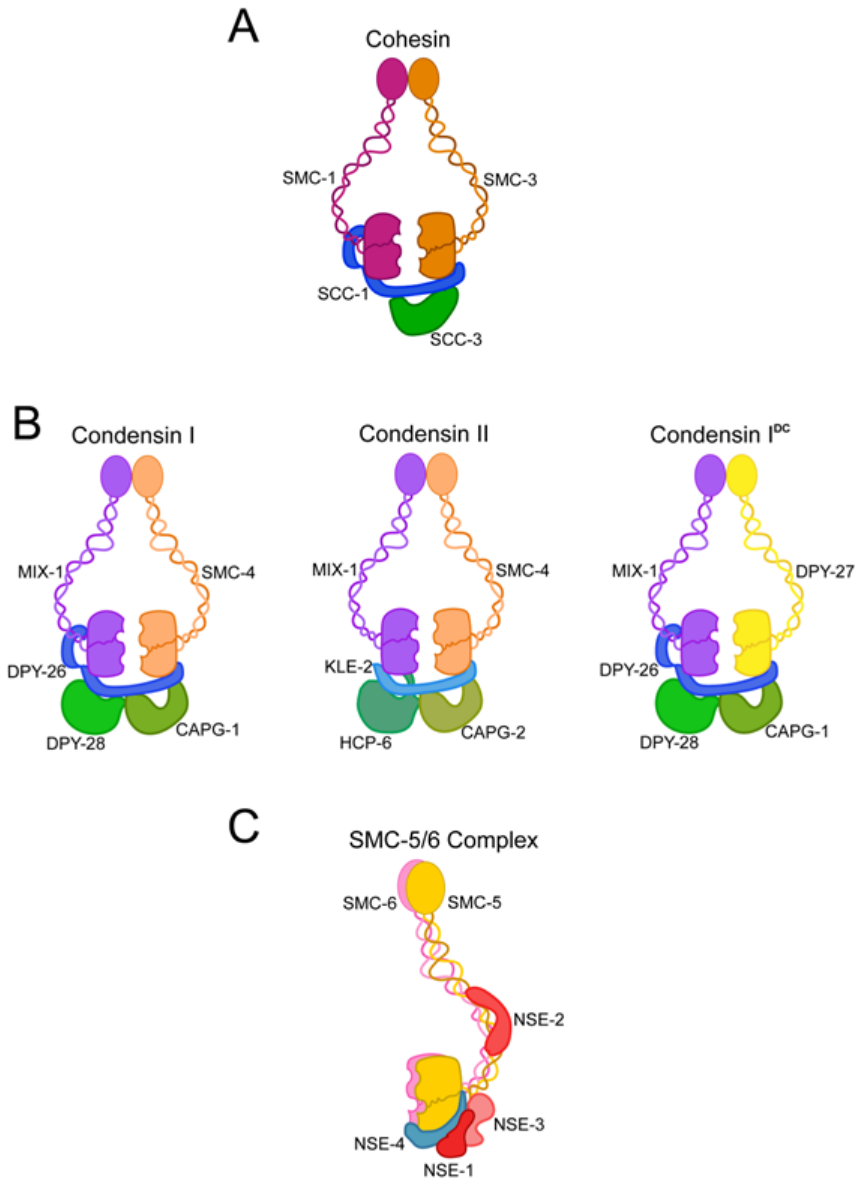

Figure 2. Chromatin motor complexes in *Caenorhabditis elegans*. SMC proteins that interact with the N-terminus of the kleisin are in pink or purple, while SMC proteins that interact with the C-terminus of the kleisin are in orange or yellow. Kleisins are in shades of blue. HAWKs are in shades of green, and Kites are in shades of red. (**A**) The 4 subunits of cohesin in the closed ring conformation, shown here with the *C. elegans* subunit names. (**B**) Condensin I, condensin II, and condensin I^{DC} are shown in the closed ring conformation, shown here with the *C. elegans* subunit names. (**C**) The SMC-5/6 complex is shown here with the characteristic "boomerang" shape and *C. elegans* subunit names.

Table 1. Cohesin mitotic and meiotic homologues, and cohesin regulator CTCF.

Organism	*C. elegans*	*Saccharomyces cerevisiae*	*Saccharomyces pombe*	Mammals	*Drosophila melanogaster*	*Xenopus*
SMC1	SMC-1	Smc1	Psm1	SMC1α, SMC1β *	DmSMC1/Smc1	XSMC1a/Smc1a XSMC1b/Smc1b
SMC3	SMC-3	Smc3	Psm3	SMC3	Cap/Smc3	XSMC3/Smc3
Kleisin	SCC-1/COH-2 COH-1 REC-8 * COH-3 * COH-4 *	Scc1/Mcd1 Rec8 *	Rad21 Rec8 *	RAD21 RAD21L * REC8 *	DRAD21/Rad21 c(2)M *	XRAD21/Rad21 XREC8/Rec8 *
HAWK	SCC-3	Scc3/Irr1	Psc3 Rec11 *	SA1/STAG1 SA2/STAG2 SA3/STAG3 *	DSA1/Sa1 SA-2/Sa2 *	XSA1/Sa1 XSA2/Sa2
CTCF	-	-	-	CTCF	DmCtcf/Ctcf	XCTCF/Ctcf

* indicates paralogues functional only during meiosis.

The full condensin complex (now called condensin I in eukaryotes) was originally found in *Xenopus* extracts, where co-immunoprecipitation using antibodies against the SMC proteins was used to pull down the non-SMC protein members of the complex [52]. These non-SMC proteins are now identified as CAP-D2, CAP-G, and CAP-H (DPY-28, CAPG-1, and DPY-26 in *C. elegans*). CAP-D2 and CAP-G are both HEAT-repeat domain containing proteins, whereas CAP-H is the kleisin [62]. The binding of the kleisin to the SMC proteins directly regulates the ATPase and loop-extruding function of the condensin. The current predicted mechanism suggests that the N-terminal tail of CAP-H relaxes its hold on SMC-2, which allows the SMC heads to work together to bind and hydrolyze ATP, opening the condensin ring to load onto DNA [63,64].

While the SMC/kleisin proteins are highly conserved from bacteria to eukaryotes, the non-SMC/kleisin regulatory proteins are not. A key difference between bacterial and eukaryotic condensins is that eukaryotic condensins have these HEAT-repeat domain containing proteins. Bacterial condensins instead have Kite (kleisin interacting winged-helix tandem elements) dimers to finish out their condensin rings with the SMC proteins and kleisin, and these Kites do not contain heat repeats [65]. Instead, the HEAT-repeat domain containing proteins found in present-day eukaryotic condensins and cohesins are now considered part of a unique subgroup of HEAT-repeat proteins; HAWKs (HEAT proteins associated with kleisins) [66]. Interestingly, these HAWKs are assumed to have replaced Kites in the condensin inherited from the last common eukaryotic ancestor [66].

Unlike cohesins that have multiple paralogous subunits to differentiate between functions, there are just two distinct condensin complexes with different functions in most eukaryotes, known as condensin I and condensin II [67]. Condensin I and II share the same SMC proteins, SMC2/4, but contain different non-SMC proteins (Figure 2B). Condensin I consists of CAP-D2, CAP-G, and CAP-H (see Table 2). Condensin II replaces those with CAP-D3, CAP-G2, and CAP H2 (see Table 3). One main difference in the two sets of non-SMC proteins is how they regulate condensin function. As mentioned previously, the ring-opening of condensin I is controlled by the kleisin CAP-H. Moreover, mitotic loading of condensin I onto DNA has been shown to be regulated by phosphorylating the N-terminal tail of CAP-H [63]. In contrast, CAP-H2 of condensin II does not have an N-terminal tail. Instead, the unique regulatory elements are found in one of the HAWK proteins, CAP-D3. CAP-D3 contains an additional helical HEAT "docker", not found in CAP-D2, that can be phosphorylated [68].

Table 2. Condensin I eukaryotic homologues.

Organism	*C. elegans*	*S. cerevisiae*	*S. pombe*	Mammals	*D. melanogaster*	*Xenopus*
SMC2	SMC-2	Smc2	Cut14	SMC2	DmSmc2/Smc2	XCAP-E/Smc2
SMC4	SMC-4 DPY-27 *	Smc4	Cut3	SMC4	DmSmc4/Smc4	XCAP-C/Smc4
Kleisin	DPY-26	Brn1	Cnd2	CAP-H	Cap-H/Barren	XCAP-H/Cap-H
HAWKs	DPY-28 CAP-G1	Ysc4 Ysc1	Cnd1 Cnd3	CAP-D2 CAP-G	dCap-D2/Cap-D2 dcap-g/Cap-G	XCAP-D2/Cap-D2 XCAP-G/Cap-G

* indicates paralogues functional only in dosage compensation.

Table 3. Condensin II homologues in eukaryotes.

Organism	*C. elegans*	Mammals	*D. melanogaster*	*Xenopus*
SMC2	SMC-2	SMC2	DmSMC2/Smc2	XCAP-E/Smc2
SMC4	SMC-4	SMC4	Glu/SMC4	XCAP-C/Smc3
Kleisin	KLE-2	CAP-H2	dCap-H2/Cap-H2	XCAP-H2/Cap-H2
HAWKs	HCP-6 CAP-G2	CAP-D3 CAP-G2	dCAP-D3/Cap-D3 -[1]	XCAP-D3/Cap-D3 XCAP-G2/Cap-G2

[1] A paralog for CAP-G2 has not been found in *D. melanogaster*.

C. elegans contain these condensins with their key structures, but unlike other eukaryotes, *C. elegans* contain three condensins. Condensin I is made up of the SMC protein pair MIX-1 (the commonly used name for *C. elegans* SMC-2) and SMC-4, along with the kleisin DPY-26 and HAWKs CAPG-1 and DPY-28. Condensin II has the same SMC pair, but with the kleisin KLE-2 and HAWKs CAPG-2 and HCP-6 [69]. The third condensin, condensin I^{DC}, is identical to condensin I, but for one subunit (Figure 2B). Instead of having the SMC pair of MIX-1 and SMC-4, it has MIX-1 and a unique SMC protein DPY-27, and it is involved in dosage compensation, which will be discussed in detail later [69].

The final SMC-protein-containing complex is a not a chromatin architecture-modifying complex. Therefore, we will only discuss it briefly here. The SMC-5/6 complex is made up of the final SMC proteins SMC-5 and SMC-6, a kleisin NSE-4, and up to five regulatory proteins (see Table 4) [70,71]. Generally, the SMC-5/6 complex functions in DNA replication, DNA repair, and silencing of extra-chromosomal DNA [72,73]. In *C. elegans*, it has been shown that the SMC-5/6 complex processes double-stranded breaks in meiosis and prevents ectopic recombination [74]. The SMC-5/6 complex does not have a ring shape and, instead, is more analogous to a "boomerang" (Figure 2C) [72]. Interestingly, some of the regulatory subunits (NSE-1-3) are Kites, which could mean that the SMC-5/6 complex diverged from other SMC complexes very early [66].

Table 4. SMC5/6 complex eukaryotic homologues.

Organism	*C. elegans*	*S. cerevisiae*	*S. pombe*	Mammals	*D. melanogaster*	*Xenopus*
SMC5	SMC-5	Smc5	Smc5/Spr18	SMC5	Smc5	XSMC5/Smc5
SMC6	SMC-6	Smc6	Smc6/Rad18	SMC6	Smc6	XSMC6/Smc6
Kleisin	NSE-4	Nse4	Nse4/Rad62	NSE4/NSMCE4	Nse4	Nse4
Kites	NSE-1 NSE-2 NSE-3	Nse1 Nse2/Mms21 Nse3	Nse1 Nse2 Nse3	NSE1/NSMCE1 NSE2/NSMCE2 NSE3/NSMCE3	Nse1 Qjt/Nse2 MAGE/Nse3	Nse1 Nse2/Nsmce2/Mms21 Nse3
Other [1]	- -	Nse5 Nse6/Kre29	Nse5 Nse6	SIMC1, SLF1 SLF2	- -	Slf1 Slf2/Fam178a

[1] Proteins in this category are not related to proteins in other SMC complexes, and homologues have not been found in all species.

3. The Unique Chromatin Architecture of *C. elegans* and the Role of Chromatin Motor Complexes in Cell Division

If chromosomes of model organisms were to be compared, most model organisms have monocentric chromosomes [75–77]. Each chromosome has only a single centromere that holds the sister chromatids together. The positioning of the centromere along the chromosome can be varied, but the centromeric DNA and its surroundings are usually condensed into heterochromatin during interphase [78]. The presence of multiple centromeres is typically a result of chromosomal rearrangements and can lead to defects in chromosome segregation [75]. However, the nematode *C. elegans* has holocentric chromosomes [79]. These holocentric chromosomes lack a single point centromere and instead have kinetochore attachments along the entire length of the chromosomes [79]. Despite this difference, *C. elegans* chromosomes follow principles of chromatin organization during interphase seen in other species [80]. Therefore, this section will highlight chromatin organization during cell division in the context of *C. elegans* while also identifying those mechanisms unique to *C. elegans*.

Holocentric chromosomes have evolved multiple times independently throughout the different phyla [79]. One hypothesis is that holocentric chromosomes having microtubule attachments along their lengths allows for the correct segregation of fragments, fusion, or translocated chromosomes [81]. However, this same physical characteristic is also the source of a meiotic conundrum. When the bivalent is formed in meiosis I, the holocentric chromosome can have spindle attachments that would pull the bivalents in multiple different directions, leading to problems in segregation [79]. Therefore, there must be an adaptation to overcome this potential pitfall. *C. elegans* accomplishes this through two approaches. The first is that *C. elegans* bivalents have only one chiasma that is closer to one end of the chromosome than the other [82–84]. This results in a cruciform-shaped bivalent, like monocentric bivalents (Figure 3B). The second adaptation is that the bivalents condense very tightly so that the short arms of the cruciform are no longer visible and the entire bivalent becomes a capsule that is pulled along the spindle [85]. Now resolved, meiosis proceeds as expected.

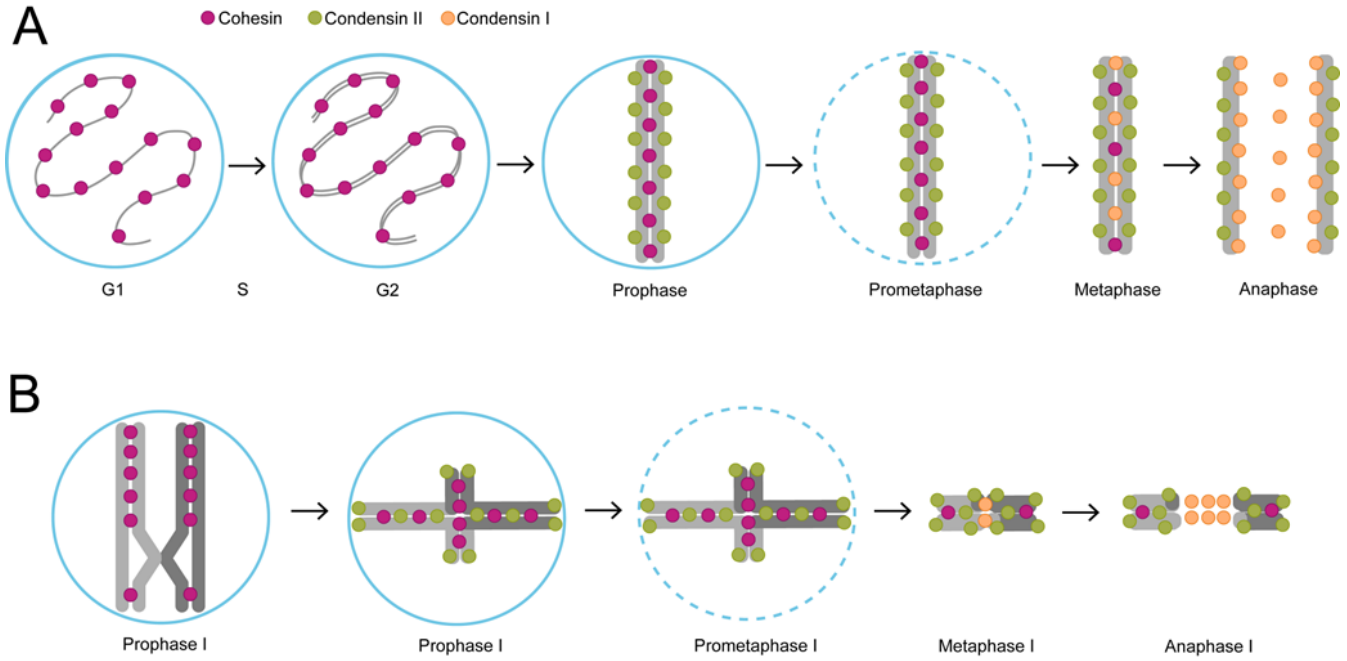

Figure 3. Chromatin motor complex localization during *C. elegans* cell division. (**A**) In mitosis, cohesin is already present on the chromosomes before S-phase. After replication, cohesin is responsible for cohesion between the sister chromatids. Condensin II localizes to the chromosomes during prophase, while condensin I localizes to the chromosomes after nuclear envelope breakdown in prometaphase.

In anaphase, cohesin is removed and a portion of condensin I moves to the spindle midzone. (**B**) In meiosis, cohesin is present along the chromosomes. After homologous recombination, condensin II localizes to the chromosomes at the end of prophase I. Condensin I localizes after nuclear envelope breakdown, specifically between the bivalents in metaphase I. In anaphase I, cohesin is removed from the bivalent short arms to allow for homolog separation and condensin I remains in the spindle midzone. Condensin II and cohesin remain on the long arm of the bivalent to keep sister chromatids attached.

What roles do the chromatin motor complexes play? Biochemical (or single-molecule) experiments with purified condensins from other organisms suggest that the mechanism that both chromatin motor complexes employ to create higher-order structures is loop extrusion [86,87]. One description of this mechanism hypothesizes that the base of the loop is captured by the ATPase heads of the SMC proteins, while the hinge grabs a further segment of DNA. Then, the hinge is "scrunched" back and transfers that DNA to the heads to create a loop [88]. Another hypothetical mechanism is that the kleisin moves and allows DNA to enter the ring of the chromatin motor complex [89], or that the DNA is pushed into the ring by an ATP-dependent "stroke" [64,90]. A final hypothetical mechanism called "reel and seal" argues that chromatin motor complexes do not hold DNA within the ring, but instead, they hold DNA at two points, the interface of the kleisin and each HAWK and that the SMC proteins "reel" more DNA and feed it into the loop [91]. While still debated, the final product of loop extrusion are those same darkly stained bodies that Walter Flemming saw in his microscope centuries ago.

After DNA replication, the two sister chromatids must be held together until metaphase where they are oriented correctly for proper migration to opposing spindle poles [61,92]. Sister chromatid cohesion is accomplished by cohesin [49,58,93–95]. The sister chromatids are contained within the cohesin ring until metaphase, when separase, a protease, cleaves the SCC-1 subunit of cohesin and releases the sister chromatids [96,97].

In meiosis, the sister chromatids must be held together, but this differs greatly from mitosis [98]. In prophase I, homologous recombination occurs, which results in crossover of non-sister chromatid arms. Once the cell reaches anaphase I, the homologues must divide. During this event, cohesin is removed from the chromatid arms distal to the chiasma but maintained at the rest of the homologues. Cohesin is still present but only maintains cohesion between the sister chromatids. Then, in metaphase II, cohesin will be completely removed from the chromatids [99]. This diversity of cohesin's roles in meiosis is accomplished through the multiple paralogues of each subunit. In *C. elegans*, the meiotic specific kleisins REC-8 and COH-3/4 replace SCC-1 [60,100,101]. Cohesins with REC-8 are recruited through a replication-dependent mechanism to the chromosomes, while cohesins with COH-3/4 are recruited during homologous recombination [60]. This is not unique to *C. elegans*. In fission yeast cohesins, the meiosis-specific kleisin Rec8 replaces Scc1, while the meiosis-specific HAWK Rec11 selectively replaces Psc3 [102,103]. Cohesin containing Psc3 is found at centromeres, but not at chromatids arms. In contrast, Rec11 forms a specific complex with Rec8 that is required for homologous recombination. Therefore, the many paralogues of cohesin subunits work together to maintain chromosome integrity during meiosis.

The condensin I and II complexes display different associations with DNA throughout the cell cycle. For example, during mitosis in mammalian cells, condensin II associates with DNA during prophase, while condensin I does not become DNA-localized until after nuclear envelope breakdown in prometaphase [104]. This is also true for *C. elegans*, where condensin II is present in the nucleus prior to nuclear envelope breakdown [105]. Metaphase onwards, condensin I and II are found in a mutually distinct pattern along the length of mammalian chromosomes [106]. In *C. elegans*, condensin I has been shown to "coat" mitotic chromosomes, whereas condensin II localizes near centromeric proteins which face the spindle poles (Figure 3A) [69,92]. Interestingly, condensin I partially shifts localization to the spindle midzone in anaphase where it delays cytokinesis to resolve

chromatin bridges [107]. Somewhat contrary to the understanding that condensins are major contributors to the condensation of DNA for cell division [5,83,92,108], it has been shown in *C. elegans* that in condensin mutants, chromosomes are still able to condense, but the lack of condensin results in segregation defects [83,92].

Condensin localization becomes even more specific in meiosis [109]. Using mammalian meiosis as a paradigm, condensin I can first be visualized in metaphase I near centromeric regions. Then, in anaphase I, condensin I localization spreads also to chromosome arms, where it stays until metaphase II. In contrast, condensin II is visible from interphase onwards. From metaphase I through metaphase II, condensin II is localized to the meiotic chromosomes, except near centromeres. These distinct localizations have been shown to be required for specific events and the successful progression of meiosis in mammals, plants, and more [109–111]. In *C. elegans*, the pattern of condensin I and II localization is similar to other organisms, where condensin II is present in prophase, but condensin I only begins to localize to the meiotic chromosomes after nuclear envelope breakdown (Figure 3B) [69,105,109]. Interestingly, in *C. elegans*, condensin I also plays a unique role in protecting cohesin from premature degradation during meiosis [112].

4. Chromatin Motor Complexes Shape Chromatin Architecture during Interphase

While chromosome territories allow for an overall view of genomic dynamics in interphase, TADs are a common unit of organization both at the broader genomic level and in more discrete single gene–enhancer interactions [113,114]. Unlike the higher strata, TADs have distinct physical features. Specifically, TADs are defined by the enrichment of cohesin and CTCF at their boundaries [21]. Unlike cell division where condesin plays a major role, it is cohesin that is responsible for the interphase chromatin architecture [108]. In mammals and *Drosophila*, cohesin continuously moves along DNA, extruding loops, until it runs into CTCF [115]. CTCF is one of the most well-known chromatin organization drivers. A transcription factor, it is expressed ubiquitously through many different tissue types. Along with other transcription factors, CTCF creates strong boundaries that cohesin cannot pass, resulting in TAD boundaries [116].

One of the largest differences in how chromatin is organized between *C. elegans* and other species is the role of cohesion and CTCF. Unlike other organisms, where cohesin and CTCF play a large role in defining chromatin architecture in interphase, this is not seen in *C. elegans*. First, a CTCF homolog has not been identified in *C. elegans* [117]. Second, there do not seem to be cohesin-defined TAD boundaries in the autosomal chromosomes [118]. Instead, *C. elegans* autosomal chromosomes have areas of high-density heterochromatin that are located at the nuclear periphery [119]. These arms are tethered by interactions between histone modifications, chromodomain reader proteins, and lamina proteins [119–122]. Regions of the chromosomes attached to the nuclear lamina are referred to as lamina-associated domains (LADs), and they have also been observed in mammalian cells, plants, and others [123,124]. Using Hi-C, it has been shown that these heterochromatin-containing autosomal arms are organized in TADs, but they are smaller than in other organisms [118]. These smaller TADs are defined by an enrichment of histone modifications. Inactive domains are enriched for H3K27me3 with a median size of 18 kb. Active domains are enriched for a variety of "active" modifications, such as H3K36me3, and have a median size of 13 kb [24,125]. These domains also interact preferentially with like-domains, reminiscent of A/B compartments [24]. Taken together, it is apparent that *C. elegans* genomic architecture utilizes familiar strategies, even without CTCF.

As for cohesin's roles in *C. elegans*, not much is known about its interphase functions. Like other eukaryotes, there are multiple SCC-1 homologs in *C. elegans*. SCC-1/COH-2 is the mitotic kleisin and SCC-1-containing cohesins are present in interphase [58], but their interphase roles have not been investigated. However, there is an SCC-1 homolog, COH-1, that plays a role in development that is not related to cell division. This protein has been observed in somatic nuclei and is consistently localized to DNA, regardless of cell cycle. Defects in COH-1-deficient worms result in muscular movement impairment,

but not mitosis [58]. Whether this somatic COH-1 is found with members of cohesin and whether that complex is involved in gene regulation are still under investigation.

The interphase localization and function of each condensin is even more varied by species and even cell type. In *Drosophila melanogaster*, it has been found that condensin I is required for proper gene expression in differentiated neurons [126]. In contrast, condensin II is required for proper chromosome territory formation in *D. melanogaster* ovarian nurse cells [127]. In human interphase cells, condensin II is found in the nucleus where it has been linked to gene regulation and cellular senescence [128], while condensin I is not nuclear [104]. In fact, condensin II has been postulated to be the main determinant of spherical chromosome territories in chordates. A study compared the chromosomal architecture of 24 eukaryotic species, representing all subphyla of chordates, and found two distinct groups of chromosomal architecture [129]. One group had spherical chromosome territories while the other had what is known as the Rabl configuration. The Rabl configuration is characterized by the clustering of all centromeres at one pole and all the telomeres at the opposite pole, resulting in chromosome arms with lengths equal to the nuclear diameter [130]. Strikingly, all the species with Rabl configuration lacked the homologs for condensin II subunits [129]. While studies seem to agree on the requirement of condensin II during interphase, the wide variety of functions, such as spatial organization between centromeres and rDNA in plants or silencing retrotransposons in *D. melanogaster*, makes it difficult to group these functions as conserved or unique [131,132].

In *C. elegans*, condensin I does not associate with chromosomes during interphase [69,105], and while condensin II is present and binds some chromosomal sites [133], its function in interphase has not been determined. However, the third condensin, condensin I^{DC}, is present. Condensin I^{DC} gets its name because it is uniquely functional in dosage compensation, where it is responsible for the unique chromatin architecture that separates the X chromosomes from the rest of the genome.

5. TADs in *C. elegans* Are a Result of Dosage Compensation

The lack of CTCF does not mean that *C. elegans* do not have any strongly defined TADs. Instead, strongly defined TADs are uniquely found on the X chromosomes [114,118]. *C. elegans* have two sexes, hermaphrodites and males, which are determined chromosomally. There are two X chromosomes in hermaphrodites, but only a single X chromosome in males [134]. This difference in chromosome copy, however, leads to a dosage imbalance between the sexes.

Imbalance in gene dosage due to sex chromosomes is common among species that have chromosomally determined sex [135–137]. In the XY system, females have two X chromosomes and are therefore homogametic, while males have an X and Y chromosome apiece and are heterogametic. Mammals, flies, some plants, and some fish use the XY system [135,136,138,139]. In the ZW system, males are the homogametic sex with two Z chromosomes, while females are the heterogametic sex with a Z and W chromosome apiece. The ZW system is used in birds, amphibians, reptiles, and others [140,141].

To overcome the gene imbalance between homogametic and heterogametic sexes, many species have evolved an adaptation known as dosage compensation. However, while the end goal is the same, the actual dosage compensation mechanisms are incredibly diverse [142]. For example, in mammals, dosage compensation is achieved through X-inactivation, where one of the two X chromosomes in XX cells is silenced [135]. In contrast, flies, despite also using the XY system, upregulate the expression of a single male X so that the gene products produced are equal to the total gene products produced in XX cells [136].

C. elegans have a completely different dosage compensation mechanism [143,144]. The dosage compensation complex (DCC) in *C. elegans* is a multi-protein complex that binds to both hermaphrodite X chromosomes, downregulating each so that the total gene products in the hermaphrodite are equal to the gene products in the male. The DCC is made up of 10 proteins (Figure 4). The first five are those of condensin I^{DC}; the SMC proteins MIX-1 and DPY-27, the kleisin DPY-26, and the regulatory HAWKs DPY-28 and CAPG-1 [69,145–147].

Then, there are three proteins, SDC-1, SDC-2, and SDC-3, which get their names from their dual roles in dosage compensation and sex determination [148–150]. The final two proteins are DPY-21 and DPY-30. DPY-21 is a jumonji-domain-containing demethylase [151,152], while DPY-30 is an essential regulator of H3K4 methylation [153–155], although its role in dosage compensation appears to be independent of its role in H3K4 methylation [156].

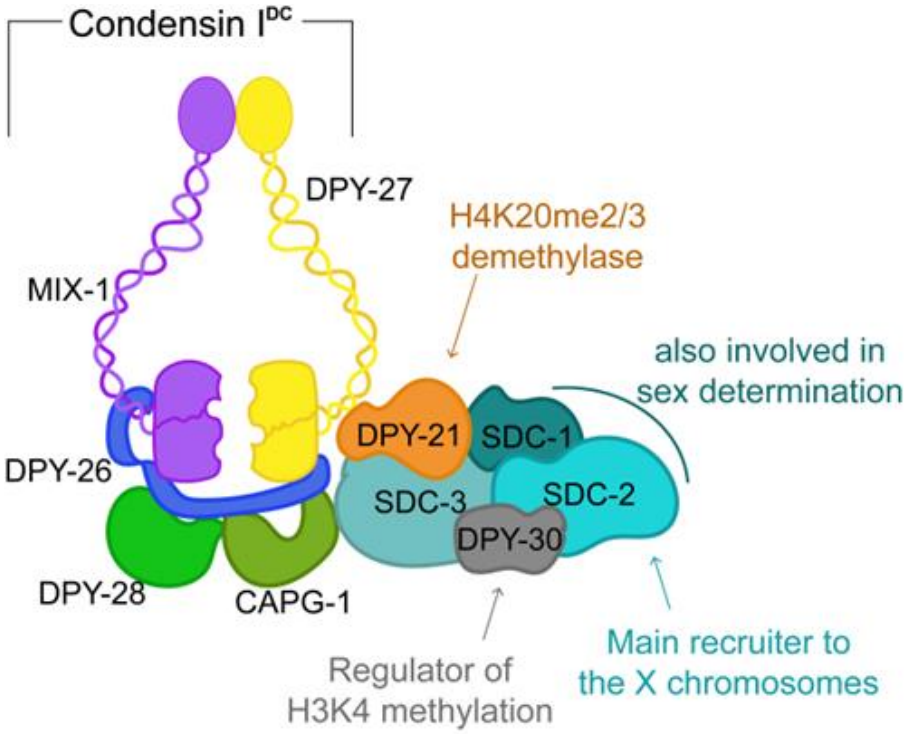

Figure 4. The *C. elegans* Dosage Compensation Complex (DCC). Condensin I^{DC} is shown with the other members of the DCC. Functions of the other members are highlighted in corresponding colors. The SDC proteins SDC-1, SDC-2, and SDC-3 are colored similarly to highlight their shared function in sex determination.

The localization of condensin I^{DC} is not subject to the cell cycle like the other condensins. Instead, it is subject to the establishment of dosage compensation. Prior to dosage compensation establishment, the members of condensin I^{DC} are not DNA-associated. Dosage compensation in *C. elegans* begins at the 30-cell stage, when SDC-2 expression begins in hermaphrodite embryos [157,158]. DCC members bind to the X chromosomes in a sequential pattern, beginning with the localization of SDC-2 to the X chromosomes [158]. It is followed by SDC-3 and DPY-30, then condensin I^{DC}, and finally SDC-1 and DPY-21 [144,145,151,153]. Once dosage compensation is established, condensin I^{DC} will be localized to the X chromosomes, regardless of cell cycle stage [69].

Localization of the DCC to the X chromosomes is dependent on *rex* sites. *rex*, or recruitment elements on X, sites are sequences of variable length that contain clusters of motifs that must act in combination to recruit the DCC [159–161]. These rex sites are distributed along the length of the X chromosomes in a non-random pattern that includes strong recruiting, weak recruiting, and non-recruiting regions based on DCC member occupancy using ChIP-seq [162]. How the DCC localizes across the X chromosomes is debated. One model is that the DCC binds initially to *rex* sites and then "spreads" to coat non-*rex* chromatin [160,163–165]. This model is supported by a ChIP-seq analysis of a fusion of the X chromosome with the fifth autosome (X:V) that demonstrates that the DCC can "spread" from the X chromosome into chromosome V [164]. However, an alternative model suggests that the *rex* sites are not recruitment elements, but they are two-sided blocks to prevent condensin I^{DC} from moving past them [166,167]. This model proposes that condensin I^{DC} is capable of loop-extruding randomly like other chromatin

motor complexes and that the *rex* sites where SDC-2 binds and prevents condensin I^{DC} from proceeding are analogous to CTCF-binding sites where CTCF prevents cohesin from looping further. Which model gives a more accurate understanding of the true mechanism is still unclear and therefore an area of ongoing work.

6. *C. elegans* Dosage Compensation as a Paradigm for Chromosome-Wide Gene Regulation

As our knowledge of chromatin organization has increased, so have developed theories of how gene regulation is no longer just about a single gene, but how the whole genome is coordinated in the context of tissue type, developmental stage, or as a response to external stressors [168–170]. Dosage compensation in *C. elegans* is an elegant paradigm for dissecting the mechanisms involved in chromosome-wide gene regulation, as the DCC is specific to X chromosomes only while also utilizing a highly conserved condensin so that the insights made in this system can be applicable broadly. Therefore, this section will highlight the many mechanisms used by the DCC to downregulate the X chromosomes.

At the gene level, binding of the DCC across the X chromosomes has been found to localize to transcriptional start sites, presumably to antagonize transcriptional machinery binding [163,171]. It has been demonstrated in many other systems that occupying the promoter region prevents the transcriptional machinery from binding and assembling [172,173].

At the nucleosome level, the DCC facilitates the post-translational modification of histone tails in multiple different ways. First, DPY-21, a member of the DCC, is responsible for the enrichment of H4K20me1 on nucleosomes of the X chromosomes [152,174,175]. This pattern is set up in a cell-cycle specific manner. First, the entire genome is stripped of H4K20me1 during DNA replication [176,177]. During mitosis, SET-1 will add H4K20me1 to the entire genome. After mitosis, that mark will be converted to H4K20me2/3 by SET-4 [174]. However, DPY-21 and the DCC will specifically convert H4K20me2 back to H4K20me1 on the X chromosome nucleosomes [143,152]. In fact, this strategy is not unique to *C. elegans*. In mammalian nuclei, the inactivated X chromosome is also enriched for H4K20me1 [178]. The other histone modification is H4K16ac, which is depleted on dosage-compensated X chromosomes and found to be associated with open chromatin [175]. A third modification which influences dosage compensation, H3K9me3, is not unique to the X chromosomes, as it is associated with any heterochromatin [121]. However, a lamina-associated chromatin reader, CEC-4, binds to H3K9me3-associated chromatin and, in cooperation with the DCC, tethers the X chromosomes to the nuclear lamina [122,179]. Tethering of heterochromatin is not unique to dosage compensation in *C. elegans* [121,122,180], but in conjunction with the DCC, it has a unique impact on the compaction and subnuclear localization of the X chromosomes. It has also been demonstrated that the nuclear RNAi machinery is also involved in X chromosome compaction and repression, but whether this effect is direct or indirect is not yet known [181]. A similar pathway involving Argonautes to establish heterochromatin has been observed in *D. melanogaster* [182]. Finally, it has been shown that one of the HAWKs, DPY-28, can interact with the tails of histone 3 and 4 [183], and this function may be a conserved one [184].

At higher-order chromatin levels, condensin I^{DC} restructures the X chromosome into strongly defined TADs, whose boundaries are demarcated by *rex* sites and DCC occupancy [118,164]. Many studies have demonstrated how condensins in other organisms are capable of DNA-dependent loop extrusion [86,185–187]. In *C. elegans*, there is also evidence of how condensin I^{DC} works in cooperation with topoisomerase I and II to create TADs [188]. Again, similar interactions between topoisomerases and chromatin motor complexes have been noted in other models [189]. At the chromosomal level, the X chromosomes in dosage compensated somatic cells are tightly condensed and located at the nuclear periphery [143,179], and the gene expression of both X chromosomes equal that of the male X [190]. The compaction and nuclear localization of the X chromosomes can be seen as a model of heterochromatic sequestering to the nuclear lamina [182].

Despite all these recent advances, there are still open questions in the field. While condensin I^{DC} is structurally equivalent to mitotic condensins, we do not have the evidence

to claim that DPY-27 is a true SMC protein. Instead, there is a possibility that condensin I^{DC} serves only as a scaffold for the rest of the DCC. If so, how does the DCC loop the X chromosomes into the distinct TADs seen in Hi-C maps? Secondly, the developmental necessity of the DCC has been demonstrated. However, whether maintenance of dosage compensation requires active function of the DCC is not known. The recognition of DPY-21 as a demethylase and its function to enrich H4K20me1 are settled. However, it has been shown that DPY-21 has a role that is independent of its jumonji domain [183]. What that role entails is not known. Finally, mutating the DCC does not cause the nuclear occupancy of the X chromosomes in hermaphrodites equal that of the male X [191]. Therefore, there may still be other mechanisms unknown, waiting to be discovered and to be added to our understanding of *C. elegans* dosage compensation. These future studies in *C. elegans* will hopefully provide insights into our larger knowledge of chromatin organization and chromosome-wide gene regulation.

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