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REVIEW ARTICLE

Regulation of loop extrusion on the interphase genome

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ABSTRACT

In the human cell nucleus, dynamically organized chromatin is the substrate for gene regulation, DNA replication, and repair. A central mechanism of DNA loop formation is an ATPase motor cohesin-mediated loop extrusion. The cohesin complexes load and unload onto the chromosome under the control of other regulators that physically interact and affect motor activity. Regulation of the dynamic loading cycle of cohesin influences not only the chromatin structure but also genome-associated human disorders and aging. This review focuses on the recently spotlighted genome organizing factors and the mechanism by which their dynamic interactions shape the genome architecture in interphase.

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Genome organization; chromatin dynamics; cohesin regulators; loop extrusion; epigenetic regulation

Introduction

Three-dimensional (3D) genome architecture and its implications have been intensively studied from a broad research area, including cancer (Deng et al. 2022; Gridina and Fishman 2022; Wang et al. 2022), nervous disorders (Pang et al. 2022; Pratt and Won 2022; van Zundert and Montecino 2022), differentiation, and development (Chen et al. 2022; Chen and Chen 2022; Cummings and Rowley 2022; Papadogkonas et al. 2022; Zhang et al. 2022). The ∼2-m-long human genome is tightly packaged in a nucleus whose diameter is <10 µm. At the same time, the genome organization should be dynamic so that numerous biochemical reactions, including gene transcription and DNA replication, can occur by a host of chromatin-associated proteins.

Genome structure is established from small to large length scale and gradually becomes higher-order structures known as topologically associated domains (TADs), compartments, and chromosome territories, depending on the length of chromosome self-interactions (Cremer and Cremer 2001; Lieberman-Aiden et al. 2009; Dixon et al. 2012; Hou et al. 2012; Nora et al. 2012; Sexton et al. 2012; Szabo et al. 2018; Kim and Yu 2020). A Hi-C is a technique to explore the 3D chromatin structure by measuring the frequency of DNA contacts genome-wide, which are visualized as a heatmap (Dekker et al. 2002; Lieberman-Aiden et al. 2009; Belton et al. 2012). On the Hi-C map, chromosome territories are shown as distinct squares along the diagonal on the genome-wide scale, and the compartments are shown as a plaid pattern up to hundreds of megabase (Szabo et al. 2019; Sikorska and Sexton 2020; Jerković and Cavalli 2021). TADs are shown as triangles along the diagonal at the scale of hundreds of kilobases to a few megabases (Szabo et al. 2019; Sikorska and Sexton 2020; Jerković and Cavalli 2021). The corner peaks of TADs in a Hi-C matrix indicate the formation of chromatin loop anchors in which enriched cohesin and CTCF protein have been identified in most mammalian cells (Rao et al. 2014; Nora et al. 2017; Szabo et al. 2019).

How these chromatin loops are formed has been an essential question in the chromosome biology field. In 2012, J. Marko's group proposed the loop extrusion model in which a loop extruder contacting two DNA regions brings the distal DNA sites into proximity using ATP and repeats the process to enlarge a DNA loop (Alipour and Marko 2012). Recent studies have revealed that cohesin is the essential motor protein for organizing interphase chromosomes through DNA loop extrusion (Davidson et al. 2019; Kim et al. 2019). Human cohesin is a ring-shaped complex comprising structural maintenance of chromosomes 1 and 3 (SMC1, SMC3), RAD21, and stromal antigen 1 or 2 (STAG1 or STAG2) (Figure 1(A)). Several factors regulating cohesin's loading cycle and loop extrusion activity have been

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A

hinge
coiled coil
SMC3
ATPase head
SMC1
RAD21
STAG1/2

	budding yeast	fission yeast	human
cohesin subunits	Smc1	Psm1	SMC1
	Smc3	Psm3	SMC3
	Scc1 (Mcd1)	Rad21	RAD21
	Scc3	Psc3	STAG1/2

B

roles	budding yeast	fission yeast	human
loading complex	Scc2	Mis4	NIPBL
	Scc4	Ssl3	MAU2
acetyltransferase	Eco1 (Ctf7)	Eso1	ESCO1/2
releasing factor	Wpl1 (Wapl)	Wpl1 (Wapl)	WAPL
releasing & stabilization	Pds5	Pds5	PDS5A/B
boundary factor	N/A	N/A	CTCF

Figure 1. The architecture of cohesin and its regulators. (A) A schematic of the human cohesin complex and a table of its ortholog constituents. Cohesin is a tetramer consisting of SMC1, SMC3, RAD21, and STAG1/2. Two SMC proteins heterodimerize via the hinge domain, and RAD21 connects the ATPase head domains. (B) A table showing the highly conserved cohesin regulators from yeast to human.

intensively investigated from yeast to human (Figure 1(B)) (Defossez and Gilson 2002; Haering and Gruber 2016; Uhlmann 2016). This review will focus on the dynamic nature of genome organization and the mechanism by which essential protein factors modify chromatin folding and influence gene expression.

Cell cycle-dependent cohesin dynamics and cohesion function

Chromosome undergoes dynamic changes every cell cycle from decondensed interphase genome structure to a highly condensed state in mitosis (Dekker 2014; Nagano et al. 2017; Miura and Hiratani 2022). On a smaller scale, TADs and compartments rapidly disappear during mitosis and reappear at the mitotic exit and entry of interphase (Naumova et al. 2013; Gibcus et al. 2018). The entire genome is duplicated identically during the S phase, and the replicated genomes are held together by sister chromatid cohesion mediated by the cohesin complex (Figure 2(A)) (Michaelis et al. 1997; Haering et al. 2008; Mehta et al. 2013; Brooker and Berkowitz 2014; Zakari et al. 2015; Litwin et al. 2018; Srinivasan et al. 2018). The cohesion starts to lose in the late prophase through a bulk of cohesin release from the condensed chromosome arms (Waizenegger et al. 2000; Liang et al. 2015; Gibcus et al. 2018). The remained centromere cohesion disappears *via* the cleavage of the RAD21 subunit by separase during the anaphase (Waizenegger et al. 2000; Hauf et al. 2001). When mitosis ends at the telophase, the chromosome begins to be decondensed (Dekker 2014). Notably, the TADs and compartments that vanished during mitosis start to reemerge and are expanded during interphase, which is correlated with the cohesin re-loading (Sumara et al. 2000; Rankin 2015; Miura and Hiratani 2022). During the G1 phase, cohesin loads onto chromatin through ATP hydrolysis, opening between two ATPase head domains (Figure 1(A)) (Lengronne 2006; Uhlmann 2016). Fluorescent-based experiments have suggested that cohesin keeps the dynamic equilibrium between association and dissociation in G1 phase, whereas it binds more stably in the S/G2 phase (Gerlich et al. 2006; Hansen et al. 2017).

Several studies have shown that cohesin complex is required to repair damaged DNA mainly by the cohesion function (Sjögren and Nasmyth 2001; Ström et al. 2004; Ünal et al. 2004). One example is an error-free double-strand break (DSB) repair mediated by homologous recombination (HR) (Figure 2(B)) (Sjögren and Nasmyth 2001; Kim et al. 2002; Schmitz et al. 2007). In the HR, one strand of the damaged

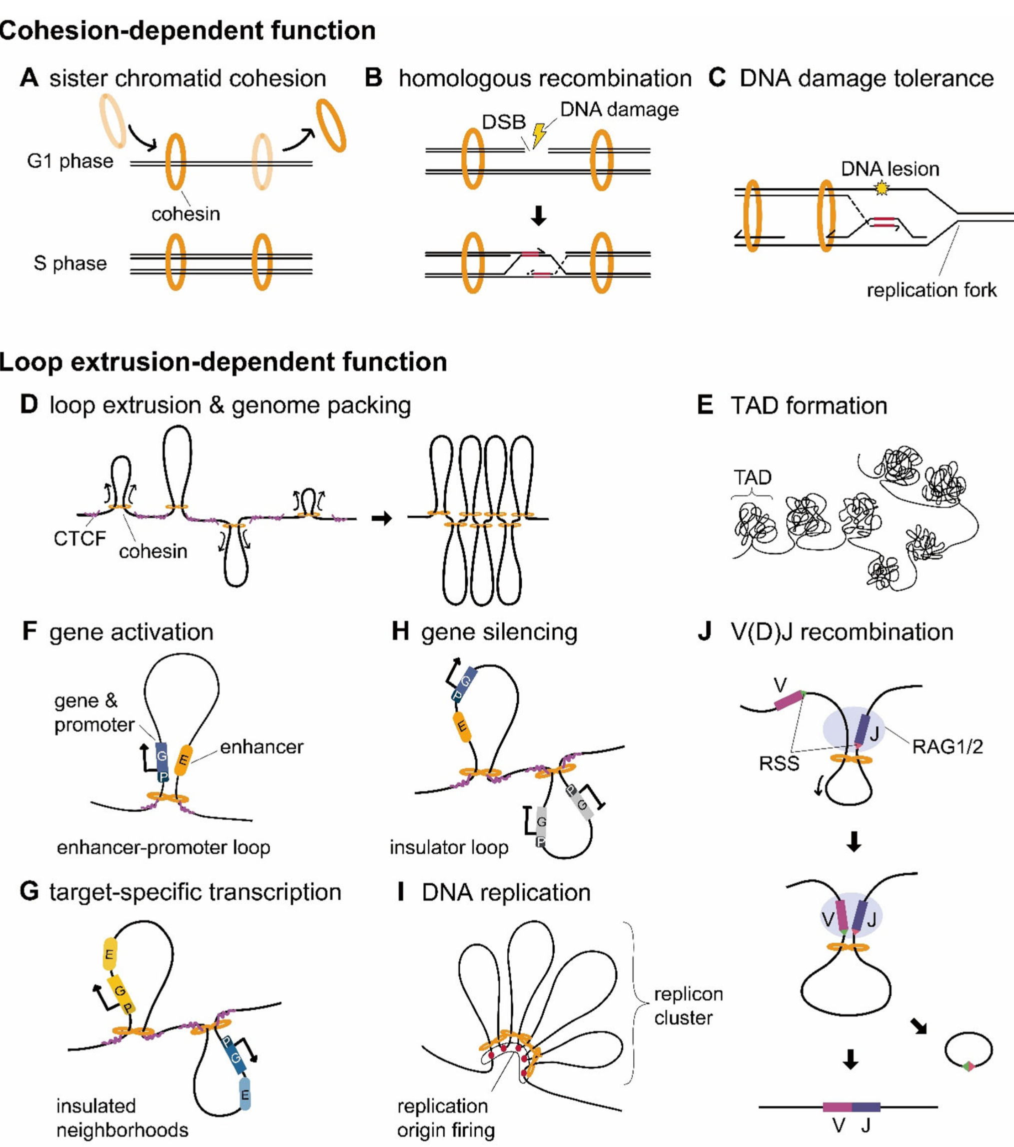

Figure 2. The cohesin functions in interphase chromatin. (A–C) Cartoons depicting cohesion-dependent roles of cohesin. (A) Cohesin dynamically loads in the G1 phase and remains stable during the S phase to tether sister chromatids together, establishing cohesion. (B) Cohesion-dependent double-stranded break (DSB) DNA repair by facilitating homologous recombination. (C) Cohesion-dependent DNA damage tolerance by aiding template switching. The DNA lesion on a single parental strand can be bypassed. (D–J) Schematics of loop extrusion-dependent functions. (D) Cohesin extrudes DNA loops and compacts the genome. (E) Cohesin-mediated loop extrusion organizes TAD structures. (F–H) Mechanisms of transcription regulation through the loop extrusion by cohesin. The formation of enhancer-promoter (E-P) loop that activates genes (F), insulated neighborhoods that activate specific target genes (G), and insulator loop that silences specific genes (H) by the cohesin motor activity. (I) DNA replication origin firing facilitated by cohesin gathered at replicon cluster. (J) V(D)J recombination can occur through cohesin-mediated loop extrusion. RAG1/2 endonucleases recognize the recombination signal sequence (RSS) and the V/J segments meet via cohesin's loop extrusion.

DNA invades an intact sister chromatid, forms a D-loop, and re-synthesizes the broken strand (Piazza et al. 2019; Shibata et al. 2020). Studies in chicken and human cells have revealed that losing chromatid cohesion decreases the HR efficiency, supporting the cohesin role in the HR (Sonoda et al. 2001; Atienza et al. 2005). Another example is the DNA damage tolerance (DDT) mechanism, in which replication machinery prefers bypassing to pausing at the damaged site when a lesion occurs during replication (Bi 2015). Cohesin behind the DNA replication fork contributes to the DDT pathway by keeping the newly synthesized strand near the sister chromatid template during a recombination-mediated bypass process (Figure 2(C)) (Fumasoni et al. 2015; Branzei 2016; Branzei and Szakal 2016).

Implications of loop extrusion by an ATPase cohesin

TADs

TAD and its boundaries are found across different cell types and species (Dixon et al. 2012; Smith et al. 2016; McArthur and Capra 2021). TADs have been described as fundamental building blocks of the interphase genome structure, which are made of chromatin loops (Dixon et al. 2012; Nora et al. 2012; Rao et al. 2014). It has shown that most TAD peaks are bound by cohesin and CTCF (Rao et al. 2014), and the depletion of cohesin-releasing factor WAPL strengthens TADs (Gassler et al. 2017; Haarhuis et al. 2017). Recent single-molecule and Hi-C studies have demonstrated that the cohesin-NIPBL complex extrudes a DNA loop and shapes the chromatin domains *via* ATPase motor activity (Figures 2(D,E)) (Davidson et al. 2019; Kim et al. 2019; Kim and Yu 2020). In the absence of cohesin, TADs and loop anchors globally disappeared, whereas compartmentalization was strengthened (Gassler et al. 2017; Schwarzer et al. 2017; Wutz et al. 2017). This opposite relationship might be due to the possibility that the cohesin-mediated looping restricts the macro-scale DNA mobility that drives compartmentalization (Haarhuis and Rowland 2017).

Gene regulation

DNA folding controls transcription in various ways: (i) gene activation by an enhancer-promoter (E-P) loop, (ii) target-specific expression through a loop called an insulated neighborhood, and (iii) gene silencing *via* an insulator loop (Figures 2(F–H)) (Chien et al. 2011; Dowen et al. 2014; Rao et al. 2014). First, the DNA loop enables a promoter to meet with its enhancer at the loop boundary site (Figure 2(F)) (Kagey et al. 2010; Rao et al. 2014; Tang et al. 2015). Second, when a local gene with its enhancer are confined inside the loop domain, it can activate the specific target gene by forming an insulated neighborhood (Figure 2(G)) (Dowen et al. 2014; Ji et al. 2016). When cohesin establishes cell-type-specific DNA loops by linking specific genes with particular enhancers, the loop leads to gene-specific transcription and defines the cell identity during differentiation (Kagey et al. 2010; Kai et al. 2018; Sasca et al. 2019). Third, an insulator loop can confine genes separately within the loop without other *cis*-regulatory elements, resulting in gene repression and silencing (Figure 2(H)) (Chien et al. 2011; Guo et al. 2018).

Interestingly, Schwarzer et al. have observed that loss of chromatin-bound cohesin by depletion of NIPBL resulted in the disappearance of TADs and associated Hi-C peaks globally without transcriptional alterations (Schwarzer et al. 2017). A study using Hi-C along with PRO-seq also has suggested that cohesin depletion altered only mild gene expression, although loop domains have vanished (Rao et al. 2017). Furthermore, a recent study investigated that the acute depletion of cohesin or cohesin regulators, such as CTCF had minimal effect on most E-P loops and transcription, suggesting that cohesin-CTCF looping is not essential for short-term maintenance of gene activation (Hsieh et al. 2022). How is the removal of cohesin-mediated E-P interactions insensitive to global gene regulation? A "time-buffering model" has also been suggested, in which established E-P interactions introduced by cohesin and CTCF are maintained by a molecular epigenetic memory even in the absence of the architectural proteins (Hsieh et al. 2022). Another possibility proposed is that cohesin-CTCF loops regulate only a small set of genes in specific biological contexts and cell types, affecting a few genomic loci (Hsieh et al. 2022).

DNA replication

Genome structure and chromatin remodeling affect DNA replication by regulating the local accessibility of replication factors, assembling replication fork, and controlling replication initiation (DePamphilis 2000; Demeret et al. 2001; Melendy and Li 2001; Aladjem 2007; Rampakakis et al. 2009; Hammond-Martel et al. 2021). Cohesin can form a replicon cluster at the replication focus, forming a stable rosette structure (Berezney et al. 2000; Cayrou et al. 2010; Sofueva and Hadjur 2012; Leonard and Méchali 2013; Fragkos et al. 2015). Cohesin-mediated loop formation facilitates replication origin firing and DNA replication initiation at a replication focus (Figure 2(I)) (Berezney et al. 2000; Cayrou et al. 2010; Leonard and Méchali 2013; Rudra and Skibbens 2013). In RAD21-depleted HeLa cells, the S phase slowed down independently of cohesion activity by reducing the fork density, indicating the decrease in the number of active origins and frequency of origin firing (Guillou et al. 2010). Moreover, cohesin interacts with the minichromosome maintenance (MCM) complex, a pre-replication protein in HeLa cells (Guillou et al. 2010). Recently, it has been proposed that the MCM complex plays as a barrier to cohesin-mediated loop extrusion by observing that MCM loss led to stronger peaks in TADs dependent on cohesin complex (Dequeker et al. 2022). Thus, cohesin interacts with the replisome components during the loop extrusion.

V(D)J recombination

Cohesin-mediated chromatin looping can mediate V(D)J recombination during lymphocyte development. V(D)J recombination occurs in B or T cell differentiation to provide a diversity of antibodies or T cell receptors (Roth 2014; Chi et al. 2020). DNA rearrangements among V (variable), D (diversity), and J (joining) gene segments generate enormous antigen receptor repertoires (Bassing et al. 2002; Roth 2014; Chi et al. 2020). The Alt group has proposed a model in which V(D)J genes are rearranged by cohesin activity in DNA loop extrusion (Figure 2(J)) (Jain et al. 2018; Zhang et al. 2019; Ba et al. 2020). RAG1/2 endonucleases bind to the (D)J segment *via* a recombination signal sequence (RSS) and then initiate chromatin scanning *via* the cohesin-mediated loop extrusion to find the V segment with another RSS. When the nucleases keep the target segments in proximity, the segments can be joined (Figure 2(J)) (Bassing et al. 2002; Hu et al. 2015; Peters 2021).

The mechanism of chromatin loop regulation

Because chromatin folding directly and indirectly influences genome integrity and human health, understanding the mechanism of 3D genome structure is essential (Misteli 2010; Krumm and Duan 2019; Anania and Lupiáñez 2020). Although a central mechanism of cohesin-driven DNA looping has been intensively documented, principles of loop regulation in the crowded nuclei are currently a spotlighted research topic. We focus on the essential regulators in the sections below by reviewing the research findings. In Figure 1(B), each nomenclature of the conserved eukaryotic proteins has been organized for clarity. In Table 1, we have summarized the key biochemical features of each factor that we will discuss in the context of 3D genome architecture.

Cohesin loaders

The cohesin association on chromatin and its residence time modulate the length scale of chromosome looping and consequently influences genome structure (Haarhuis et al. 2017; Schwarzer et al. 2017; Wutz et al. 2017; 2020). Scc2 was initially identified in budding yeast approximately three decades ago, and later its orthologs have been found in various organisms, including human (Furuya et al. 1998; Gillespie and Hirano 2004; Rollins et al. 2004; Tonkin et al. 2004). The human ortholog NIPBL was identified from its mutation in Cornelia de Lange syndrome, a rare disorder characterized by slow growth, intellectual disability, and malformation of the face/limbs (Tonkin et al. 2004). A study using immunoprecipitation and mass spectrometry in budding yeast found Scc4 that physically interacts with Scc2 (Ciosk et al. 2000). Its ortholog MAU2 was found in *Caenorhabditis elegans* and human using PSI-BLAST analysis (Seitan et al. 2006; Watrin et al. 2006).

It has been established that the Nipped-B-like protein (NIPBL)-MAU2 serves as a loader complex that promotes cohesin loading through binding to RAD21 (Figure 3(A)) (Hara et al. 2014; Shi et al. 2020). The importance of the NIPBL-MAU2 loader has been further evidenced by the observations that TADs and loops disappeared in *Nipbl*-deleted mouse liver cells (Schwarzer et al. 2017), and HAP1 cells depleting MAU2 displayed shorter loops than wild-type (Haarhuis et al. 2017). Also, a single-molecule experiment has shown that the cohesin-mediated loop formation depends on the NIPBL-MAU2 complex (Davidson et al. 2019). Furthermore, Bauer et al. have proposed a "swing and clamp" model in which NIPBL holds DNA during the loop extrusion, and the DNA bound by the hinge of cohesin moves to the ATPase heads by folding the SMC coiled-coil (Bauer et al. 2021). ATP binding transfers NIPBL from the hinge to the SMC3 head, and cohesin clasps the DNA, consequently mediating the loop extrusion (Bauer et al. 2021). Several studies have suggested that NIPBL only is enough for cohesin loading in numerous organisms, and in particular, the C-terminal fragment of human NIPBL (residues 1163 to 2804) seems to be sufficient for cohesin loading and loop extrusion (Haarhuis et al. 2017; Kim et al. 2019). In conclusion, the NIPBL-MAU2 complex, especially NIPBL, is an essential regulator in cohesin loading and loop extrusion, leading to the TAD formation (Rhodes et al. 2017; Petela et al. 2018; Kim et al. 2019).

Cohesin stabilizers

Cohesion stabilization during interphase requires SMC3 acetylation on the conserved lysine residues (K105 and K106 in humans) by ESCO1/2 acetyltransferases (Zhang et al. 2008; Nishiyama et al. 2010; Ladurner et al. 2014; Alomer et al. 2017; van Schie and de Lange 2021). Whereas ESCO1 acetylates cohesin during the G1 phase and throughout the interphase, ESCO2 mainly functions in the S phase (Minamino et al. 2015; Alomer et al. 2017; Wutz et al. 2020). The acetylated cohesin for the S phase cohesion recruits sororin and antagonizes the releasing factor WAPL (Rankin et al. 2005; Schmitz et al. 2007; Nishiyama et al. 2010; Ladurner et al. 2014). On the other hand, studies of ESCO1 using X-ray

Table 1. The structural domains and brief features of the DNA loop regulators.

Factor		Features	References
NIPBL-MAU2	M.W.	NIPBL 316 kDa, MAU2 69 kDa	Watrin et al. 2006; Davidson and Peters 2021; Panarotto et al. 2022 García-Gutiérrez and García-Domínguez 2021
	Domains	NIPBL: MAU2 interaction (1–300), Q-rich (418–462), PETPK repeats (699–764), HEAT repeats (1761–2350), 2804	
		MAU2: NIPBL interaction (1–115), 613	Seitan et al. 2006
	Oligomeric state	Heterodimer by *in vitro* purification	Bermudez et al. 2012
		Heterodimer *in vivo* mammalian two-hybrid assay (NIPBL 1–300 a.a., full-length MAU2)	Parenti et al. 2020
ESCO1	M.W.	95 kDa	
	Domains	PIP box, ZF, ACT (654–836), 840 PIP box: PCNA-interacting protein box ACT: acetyltransferase	Alomer et al. 2017; Kouznetsova et al. 2016
	Oligomeric state	Dimer by X-ray crystallography (ACT domain)	Kouznetsova et al. 2016
		Dimer by small-angle X-ray scattering (ACT domain)	
		Monomer by sedimentation equilibrium analysis and gel filtration chromatography (599–825 a.a.)	Rivera-Colón et al. 2016
WAPL	M.W.	133kDa	Gandhi et al. 2006
	Domains	YSR, FGF, Middle, C-terminus (601–1190)	Ouyang et al. 2016
	Oligomeric state	Monomer by size-exclusion chromatography coupled with multiangle light scattering (631–1190 a.a.)	Ouyang et al. 2013
PDS5	M.W.	PDS5A 150 kDa, PDS5B 165 kDa	Losada et al. 2005
	Domains	HEAT repeats; 1337 (PDS5A), 1447 (PDS5B)	Zhang et al. 2021; Losada et al. 2005
	Oligomeric state	Dimer by immunoprecipitation (*Drosophila* Pds5)	Kusch 2015
CTCF	M.W.	82 kDa	Quitschke et al. 2000; Kim et al. 2015
	Domains	ZF 1-11 (264–583), 727	Hashimoto et al. 2017; Yin et al. 2017
	Oligomeric state	Monomer in crystal by X-ray crystallography (ZFs 4–8)	Yin et al. 2017
		Monomer in solution by static light scattering (ZFs 4–11 with C-terminus)	
		Monomer in blocking cohesin-mediated loop extrusion by photobleaching analysis at single-molecule level	Davidson 2022
		Dimer or multimer by *in vivo* yeast two-hybrid assay	Yusufzai et al. 2004
		RNA-dependent dimer or multimer by GST pull-down assay	Saldaña-Meyer et al. 2014
		Cluster containing ∼6–8 CTCF by *in vivo* photobleaching analysis with super-resolution imaging	Lee et al. 2022
		Cluster containing ∼2–8 CTCF by *in vivo* photobleaching analysis with super-resolution imaging (Mouse CTCF)	Gu et al. 2020

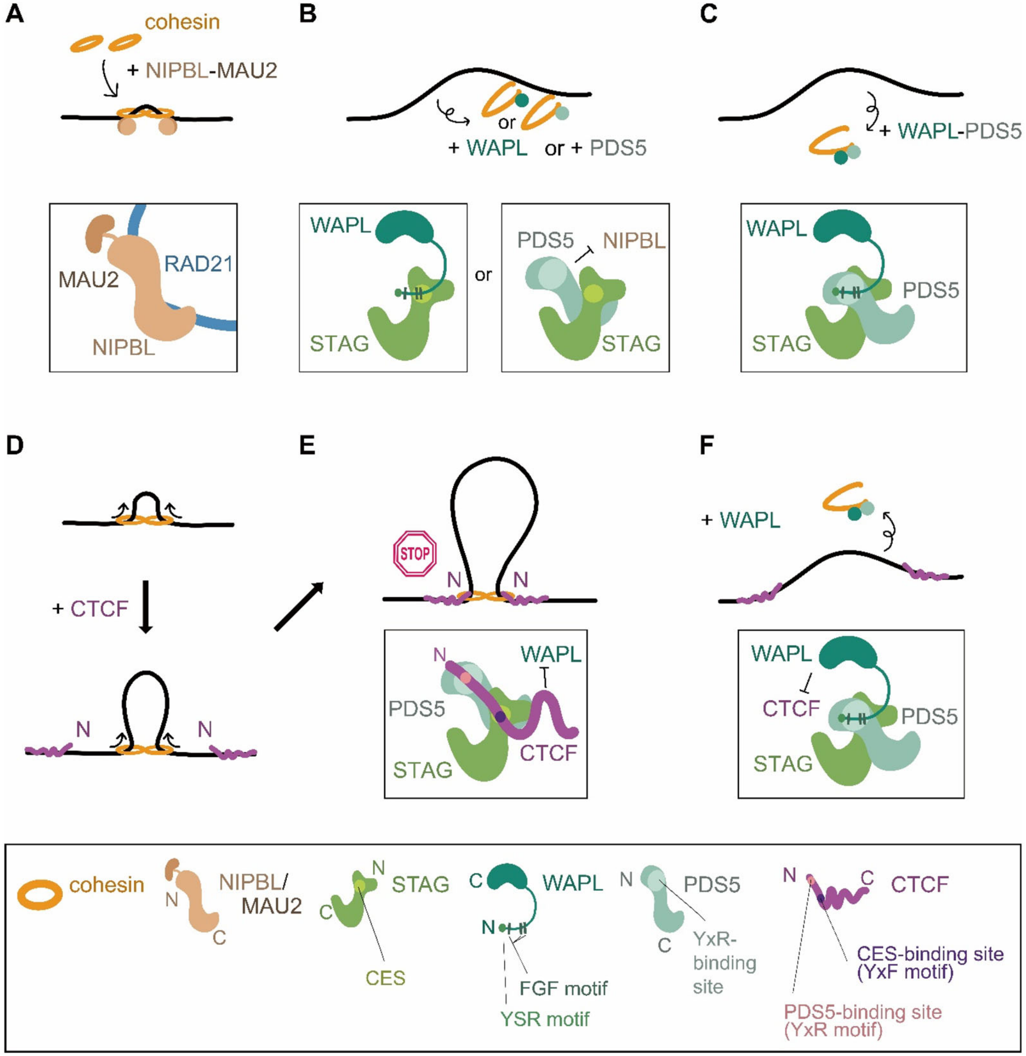

Figure 3. The physical and functional relationship between loop regulators during cohesin-mediated loop extrusion. (A) NIPBL-MAU2 complex binds to RAD21 and facilitates cohesin loading. (B) WAPL or PDS5 can release cohesin. The N-terminal region of WAPL contains the YSR and two FGF motifs that bind to RAD21/STAG interface called conserved essential surface (CES) (Ouyang et al. 2013). The C-terminus of PDS5 also binds to the CES of STAG subunit (Hons et al. 2016). PDS5 competes against NIPBL to bind cohesin, causing cohesin release. (C) The WAPL-PDS5 complex unloads the cohesin more efficiently than each factor solely. (D) Cohesin extrudes DNA until it contacts the convergent CTCF sites. (E) The N-terminus of CTCF interacts with cohesin to stop loop extrusion. The YxF and YxR motifs on the CTCF N-terminus bind to the STAG and PDS5, respectively (Li et al. 2020; Nora et al. 2020; van Ruiten and Rowland 2021). WAPL and CTCF compete for the binding of STAG and PDS5. (F) WAPL and PDS5 form a complex to release cohesin complex and antagonize CTCF-cohesin interaction.

crystallography have identified an acetyltransferase domain (ACT) and a unique structure that binds to SMC3 (Table 1) (Kouznetsova et al. 2016; Rivera-Colón et al. 2016). A study using iFRAP and Hi-C has shown that the SMC3 acetylation by ESCO1 extends the residence time of cohesin up to hours, enabling the formation of long-lived loops (Wutz et al. 2020). Also, the comparison between acetylated SMC3 ChIP-seq profiles and the Hi-C maps has demonstrated that the acetylated cohesin complexes are abundant in chromatin anchors, suggesting the role of ESCO1 in setting the loop boundaries (Rahman et al. 2015; Wutz et al. 2020).

Boosters for chromatin folding dynamics

The dynamic dissociation of cohesin from chromatin is necessary to control chromatin folding in a timely fashion. If cohesin stays on chromatin permanently, the abnormal cohesin stabilization leads to genome instability and human diseases (Oikawa et al. 2004; Ohbayashi et al. 2007; Zhang et al. 2021). An essential regulator for the cohesin release is wings apart-like protein (WAPL). WAPL opens the cohesin's exit gate between the nucleotide-binding domain of SMC3 and the N-terminus of RAD21, leading to cohesin dissociation from DNA (Figure 3(B)) (Chan et al. 2012; Buheitel

and Stemmann 2013). WAPL depletion in mice stabilized the cohesin interaction on chromatin by extending the residence time of cohesin over twenty-fold (Tedeschi et al. 2013). The aberrantly stabilized cohesin by WAPL depletion gives a higher chance of loop extrusion, resulting in extended chromatin loops and increased contacts nearby TADs (Haarhuis et al. 2017; Wutz et al. 2017). The abnormally elongated axial structure was first observed in the nucleus of WAPL-depleted mouse embryonic fibroblasts (MEFs) (Tedeschi et al. 2013). Immunofluorescence microscopy also showed that cohesin accumulates in axial structure in WAPL-depleted HeLa cells in the G1 phase (Wutz et al. 2017). WAPL depletion in the G1 phase of human colorectal carcinoma cells also displayed increased interdomain contacts in a cohesin-dependent fashion (Luppino et al. 2020). The significance of WAPL has been demonstrated that WAPL generates a free cohesin pool, which facilitates cohesin redistribution and the formation of an E-P loop to increase gene expression on cell-type-specific regions (Liu et al. 2021).

Along with WAPL, precocious dissociation of sisters protein 5 (PDS5) plays a role in cohesin release (Figure 3(B)). Studies using FRAP have shown that cohesin's residence time increased about 2.5 times more in PDS5A/B-depleted MEFs and HeLa cells (Ouyang et al. 2016; Wutz et al. 2017; Morales et al. 2020). PDS5 can inhibit cohesin loading by competing with NIPBL for binding to RAD21 (Figure 3(B)). The crystal structure of Scc2 from the thermophilic fungus *Chaetomium thermophilum* have directly shown that Pds5 and Scc2 are competitive because their binding sites on Scc1 overlap (Kikuchi et al. 2016). Also, the binding of a cofactor IP_6 to PDS5 disturbs the interaction between SMC3 and RAD21 and leaves the cohesin's ring opened, which can increase the pool of dynamic cohesin (Ouyang et al. 2016). Notably, PDS5 forms a heterodimer with WAPL and cooperates to unload the cohesin more efficiently (Figure 3(C)). When fission yeast Wapl and Pds5 were mixed in identical molar amounts, they were purified in the same fraction during gel filtration (Murayama and Uhlmann 2015). WAPL interacts with the N-terminus of PDS5 through its YSR motif and two FGF motifs (Figure 3(C)) (Shintomi and Hirano 2009; Huis In 't Veld et al. 2014; Ouyang et al. 2016). Various deletion combinations of WAPL and PDS5A/B in G1-phase HeLa cells showed that the WAPL-PDS5 complex is a much more effective unloader than each factor solely (Wutz et al. 2017). When deleting both WAPL and PDS5A/B, a distinct axial structure was displayed, and TAD size dramatically expanded compared with the depletion of either WAPL or PDS5A/B by itself (Wutz et al. 2017).

On the other hand, PDS5 paradoxically facilitates cohesin loading by mediating SMC3 acetylation (Carretero et al. 2013; Muir et al. 2016). PDS5A/B-double-knockout MEFs displayed a noticeable reduction of acetylation of SMC3 (Carretero et al. 2013). Deletion of either PDS5A or PDS5B also decreases the acetylated SMC3 partially (Carretero et al. 2013). Then, what is the benefit of having two factors-WAPL and PDS5 for cohesin unloading, even one factor can play an opposite role? It may help to adjust the cohesin unloading level in a sophisticated manner for dynamic chromatin folding. Moreover, if PDS5 remains on chromatin-bound cohesin after playing a role in the loading, the subsequent unloading process would be able to occur promptly.

Loop boundaries

The structures, such as DNA loops and TADs essentially possess an anchoring point that distal DNA sites meet. Where and how does the cohesin-mediated loop extrusion halt at such boundaries? To date, the CCCTC-binding factor (CTCF) is a central physical barrier to the cohesin translocation and TADs formation (Dixon et al. 2012; Ong and Corces 2014; Rao et al. 2014; Zhang et al. 2022). CTCF was first identified and isolated as a protein with 11 zinc fingers (ZF) that contacts a proximal region of the *c-myc* gene's promoter in chicken cells (see CTCF in Table 1) (Lobanenkov et al. 1990; Klenova et al. 1993). CTCF is a sequence-specific binding factor, localized on the three repeated CCCTC sequences with regular interval nucleotides (Lobanenkov et al. 1990). Mice and human CTCF have been found afterward (Filippova et al. 1996). Although CTCF is conserved in most higher eukaryotes, it is absent in yeast, *C. elegans*, and plants (Heger et al. 2012).

CTCF was initially characterized as a transcription factor, which can activate genes by interacting with the large subunit of RNA Polymerase II *via* its C-terminal domain (Chernukhin et al. 2007). In addition, CTCF mediates gene activation by promoting the interaction between the enhancer and promoter through the DNA loop (Kagey et al. 2010; Faure et al. 2012). The CTCF loop can also repress gene expression by confining either an enhancer or promoter inside the loop (Guo et al. 2018). For example, deleting the CTCF led to increased expression of repressed specific genes within the prostate cancer risk-associated loops, indicating the role of CTCF in oncogene suppression (Guo et al. 2018).

During the loop extrusion, the prominent role of CTCF is to set the boundary of the loops (Figures 2(D), 3(D,E)) (Cuddapah et al. 2009; Dixon et al. 2012). CTCF is enriched in the loop anchors and TAD boundaries (Dixon et al. 2012; Rao et al. 2014). CTCF depletion hindered the cohesin from localizing at the CTCF binding sites in human cells, whereas cohesin depletion by siRNA did not affect the CTCF binding (Parelho et al. 2008). Also, CTCF depletion by auxin degradation in G1-phase HeLa cells diminished most DNA loops and blurred TAD boundaries (Wutz et al. 2017). Likewise, CTCF knockdown by RNAi increased the spatial overlap and interaction between chromatin domains (Luppino et al. 2020). Thus, CTCF is crucial for setting clear TAD boundaries.

A seminal feature of CTCF is its polarity: In the TAD boundaries, the percentage of convergent (Forward-Reverse) CTCF pairs is considerably higher than other types of CTCF orientation, including divergent (Reverse-Forward), tandem rightward (Forward-Forward), and tandem leftward (Reverse-Reverse) (Rao et al. 2014; Guo et al. 2015; Tang et al. 2015; Dawson et al. 2020). The orientation preference has been further demonstrated by the observation that depletion of convergent CTCF binding sites causes chromatin loops to disappear, and the loops did not restore even after tandem CTCF sequences were inserted (de Wit et al. 2015). Moreover, computational simulation using CTCF ChIP-seq following the CTCF convergent rule reproduced the Hi-C contact map (Sanborn et al. 2015). However, not all convergent CTCF binding sites form DNA loops. Even though the ratio is comparably low, about 20–30% of the loops follow a tandem CTCF manner, and about 2% account for the divergent CTCF pairs (Guo et al. 2015; Tang et al. 2015).

How can CTCF become the loop boundaries? When each N-terminus of CTCF can interact with a conserved essential surface (CES) on the STAG subunit, CTCF blocks the cohesin loop extrusion (Figure 3(E)) (Pezzi et al. 2000; Hara et al. 2014; Pugacheva et al. 2020). CTCF stabilizes the formed loops by binding to STAG, which antagonizes WAPL binding to cohesin (Figure 3(E)) (Li et al. 2020; Nora et al. 2020). CTCF competes with WAPL for binding to PDS5, that is associated with WAPL to release the CTCF-cohesin loops (Figure 3(F)) (Nora et al. 2020).

Interestingly, CTCF can bind to RNA, and the CTCF-RNA complex can form CTCF clusters and influence 3D chromatin structure (Saldaña-Meyer et al. 2014; Hansen et al. 2019; Saldaña-Meyer et al. 2019; Oh et al. 2021). The RNA binding region (RBR) in CTCF includes ZF10-11 and the C-terminus, which is clearly distinct from the DNA-binding domain in ZF3-7 region (Saldaña-Meyer et al. 2014; Hashimoto et al. 2017; Saldaña-Meyer et al. 2019). A recent study by Hansen et al. has identified the internal RBR (RBR_i) region spanning the C-terminal to ZF11, and demonstrated its role in CTCF clustering by super-resolution imaging of cells expressing RBR_i-depleted mutant (Hansen et al. 2019). Also, RBR mutation significantly disrupts the chromatin binding of CTCF, decreases the ability of loop formation, and changes the chromatin structure and gene expression profile (Saldaña-Meyer et al. 2019). A newly developed deep learning model called DeepLncCTCF discovered the novel CTCF-binding RNA motif in human and identified about 5000 candidates of lncRNA for potential CTCF binding (Kuang and Wang 2020; Soibam 2022). Oh et al. have shown that the Jpx lncRNA can expel low-affinity CTCF *via* competitive inhibition, suggesting the critical role of lncRNA in selecting anchor sites and affecting 3D chromatin architecture and gene expression (Figures 4(A,B)) (Oh et al. 2021).

Several studies have found other barriers to cohesin movement besides CTCF. RNA polymerase (RNAP) can be a moving barrier that relocalizes the cohesin complex (Figure 4(C)) (Banigan et al. 2022). RNAP inhibition diminishes the loop extrusion boundaries and consequently triggers the formation of new long-range *cis* interaction (Jeppsson et al. 2022). Also, the observation that a high level of transcription leads to the loss of loops supports the idea that transcription antagonizes the cohesin-mediated loop extrusion (Reed et al. 2022). A single-molecule study has suggested that multiple R-loops act as a cohesin barrier, and a single R-loop slows down the translocation (Zhang et al. 2022). In addition, Jeppsson et al. have shown that the stalled DNA replication fork and transcription jointly restrict the loop extrusion during the S phase (Jeppsson et al. 2022). The MCM protein of a pre-replication complex has been shown to serve as a physical barrier through single-molecule imaging (Figure 4(D)) (Dequeker et al. 2022). Lastly, lncRNA, such as *HOTTIP* can regulate TAD structure by interacting with the CTCF/cohesin complex and forming an R-loop, setting the TAD boundaries (Luo et al. 2022). Together, diverse mechanistic factors can be a barrier to cohesin-mediated loop extrusion.

Cohesin's functional state

In which form does cohesin work *in vivo*? Does cohesin work as a monomer or dimer/oligomer? This information is important because the pattern of the loop extrusion changes depending on the cohesin's state (Hassler et al. 2018). By counting the number of photobleaching steps at the single-molecule level, two research groups

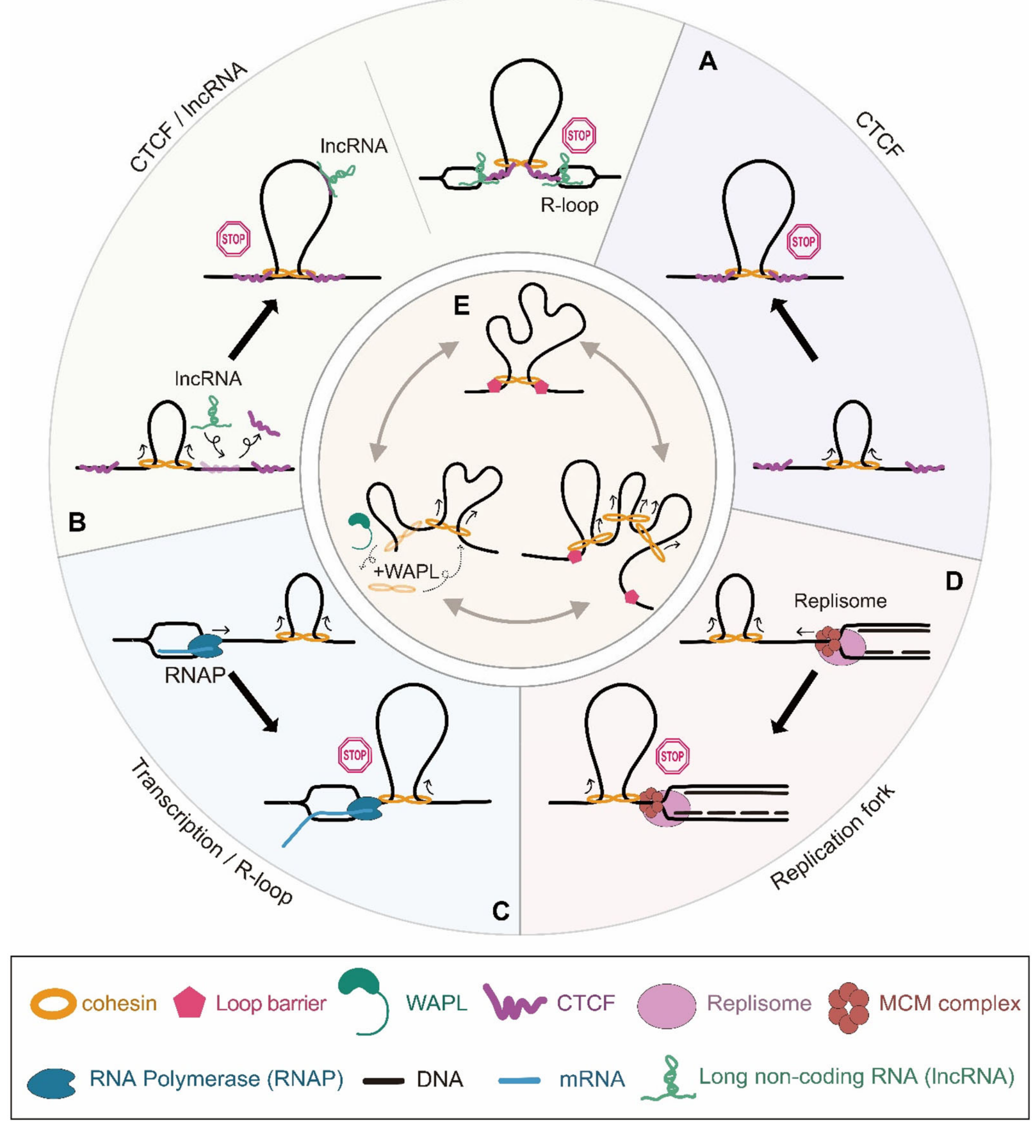

Figure 4. The dynamic regulation of DNA loop extrusion. (A) CTCF is the general boundary factor regulating the loop extrusion. (B) lncRNA can mediate the loop dynamics by detaching CTCF from chromatin, thereby determining the sites of loop anchors (Oh et al. 2021). Also, lncRNA can form R loops that reinforce CTCF boundaries and TAD formation (Luo et al. 2022). (C) Transcription constituents including RNA polymerase (RNAP) or R-loop can hinder loop extrusion. (D) Components of the stalled replication fork, such as MCM helicase can block the cohesin translocation (Dequeker et al. 2022). (E) The model describing the dynamic nature of cohesin-mediated looping. WAPL facilitates loop dynamics, which the loop rarely exists in a stable state and is mainly in a transient state.

reported that cohesin plays as a monomer or dimer during loop extrusion (Davidson et al. 2019; Kim et al. 2019). On the other hand, in a study using Halo-V5-Rad21 knock-in mouse cells in which half allele still contains wide-type Rad21, the wild-type cohesin was detected upon co-IP, suggesting that cohesin exists as dimer or oligomer in mammalian cells (Cattoglio et al. 2019). It has been speculated that cohesin functions as a dimer given that each monomer could reel in the DNA symmetrically or asymmetrically and interact with each CTCF (Kim and Yu 2020). Then how would two cohesin molecules interact? Two possible scenarios have been suggested: the “monomeric ring” and the “handcuff” model. The STAG subunit is shared in the handcuff dimer form (Zhang et al. 2008; Nasmyth 2011; Hassler et al. 2018). A study that determined the stoichiometry between the cohesin subunits (SMC1:SMC3:RAD21:STAG1/2) reported a 1:1:1:1 ratio, supporting the monomeric ring scenario that does not share any subunit (Holzmann et al. 2019).

Recently, super-resolution imaging in mESCs showed that cohesin forms clusters, mostly overlapping with the CTCF clusters, indicating spatial coupling between cohesin and CTCF (Hansen et al. 2017; Gu et al. 2020).

5–15 cohesin molecules comprise the cluster whose coupling distance with CTCF is ∼60 nm, which correlates with cohesin ring size (Gu et al. 2020). Also, Ryu et al. directly observed that yeast cohesin accumulates to form a compacted cohesin-DNA cluster containing several hundreds of cohesin complex by single-molecule and AFM imaging (Ryu et al. 2021). Also, an *in vivo* experiment using proximity-dependent biotinylation labeling supported the model of cohesin-mediated DNA cluster (Xiang and Koshland 2021). Although the functional relationship between the cohesin cluster and loop extrusion needs further investigation, the cohesin cluster formation could be facilitated by its motor activity at a focal genomic site.

Loop extrusion, boundaries, and dynamic chromatin folding

The chromatin domains are generally thought to be stable structures, but recent pioneering research has demonstrated its significant dynamic characteristic (Hansen et al. 2017; Gabriele et al. 2022; Mach et al. 2022). The cohesin and CTCF bind to chromatin transiently and exchange rapidly, which leads to high loop dynamics (Figure 4(E)) (Hansen et al. 2017). The residence time of CTCF and cohesin measured by single-molecule imaging *in vivo* was about 1 or 22 min, respectively (Hansen et al. 2017). It also has shown that CTCF takes about 1 min to rebind on another site, whereas cohesin takes about 30 minutes (Hansen et al. 2017). Recently, Gabriele et al. investigated the dynamic nature of chromatin loops by visualizing two fluorescently labeled CTCF boundaries of the 505-kb *Fbn2* TAD in mES cells (Gabriele et al. 2022). Their image analysis from the 3D trajectories has revealed that a fully looped state resists for 10–30 min and even appears only 3% of the time, suggesting that the loops mainly exist as a partially extruded form (Gabriele et al. 2022). Another group also quantified *in vivo* loop dynamics by imaging two chromosomal locations separated by 150-kb within a TAD, representing the duration time of CTCF-anchored loops to be about 5–15 min on average (Mach et al. 2022). Such quantitative measurement of the chromosome folding dynamics provides insight for a fundamental mechanistic principle controlling the temporal constraints of the genome folding bearing with the spatial confinement of the nucleus (Gabriele et al. 2022; Mach et al. 2022).

Guo et al. have quantitatively characterized cohesin-propelled looping dynamics using quiescent primary lymphocytes and revealed the formation of jet-like projections from the Hi-C maps (Guo et al. 2022). They found that the jet-like structures can expand symmetrically up to 1–2 Mb without unilateral CTCF constraint inhibiting the jet propagation and converting to asymmetric extrusion, suggesting the independent regulation of loop extrusion in both directions (Guo et al. 2022). Another recent study from Dekker group has suggested two distinct modes of extruding cohesin complex using an engineered cohesin harboring cleavable RAD21 by TEV protease (Liu and Dekker 2022). The Hi-C maps indicated that intra-TAD chromatin contacts remained stable upon RAD21 cleavage in contrast to the sensitivity of CTCF-CTCF loops. These findings imply the importance of cohesin ring integrity and topological binding for the loops at TAD boundaries, suggesting the model by which changes in cohesin conformation and subunit exchange occur during loop extrusion (Liu and Dekker 2022). Given that additional factors including transcription, R-loops, or stalled replication fork can serve as barriers to cohesin movement, asymmetric or transient loop extrusion might be widely present on the genome, which facilitates the dynamics of chromatin folding (Figure 4) (Banigan et al. 2022; Dequeker et al. 2022; Luo et al. 2022; Zhang et al. 2022).

What are the advantages of having such dynamic looping in the nucleus? Liu et al. have shown that cohesin stabilization caused by WAPL depletion leads to a loss of cohesin in certain gene regions related to an early embryonic stage, reduction of intra-TAD DNA contacts, and depression of the gene expression, suggesting that a dynamic cohesin pool depends on cohesin turnover (Liu et al. 2021). We speculate that the loop dynamic facilitates scanning of the E-P interaction through the process of rapid cycle of loop formation. The repetitive cycle of forming and collapsing the loop would increase the heterogeneity of chromatin contacts in response to the extranuclear stimuli. The rapid CTCF turnover would also determine where the loop anchors to regulate transcription, which can be supported by the observation that CTCF can be removed from chromatin by lncRNA (Oh et al. 2021).

Perspective

3D genome organization driven by the ATPase motor cohesin has been extensively documented in past years. It has been established that cohesin extrudes chromatin loops, forming the basic unit TAD structure. Studies of regulators controlling the loading cycle and translocation of cohesin provide insight into how loop extrusion and chromatin folding are dynamically regulated.

Many important questions still need further investigation. Why does cohesin suppress compartmentalization while it facilitates TAD formation? Which form of cohesin extrudes chromatin *in vivo*? How does cohesin loop extrusion affect clustering or vice versa? How does the cohesin conformation change at the anchoring site and during the middle of loop extrusion? It would be also interesting to see what can be the distinct boundary factors related to a specific biological process, such as DNA repair system. The RNA effects on TAD boundaries and 3D genome architecture are also intriguing subjects. It is attractive to reveal how PDS5 can perform opposite roles and how SMC3 acetylation affects WAPL-PDS5 activity at the boundaries. It will be interesting to see how the releasing factor regulates cohesin redistribution and loop dynamics at the single-molecule level. Answering these questions will provide considerable insight into the mechanism of interphase chromatin structure dynamics.

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