MIT Libraries | DSpace@MIT

MIT Open Access Articles

SMC complexes link gene expression and genome architecture

The MIT Faculty has made this article openly available. ***Please share*** how this access benefits you. Your story matters.

Citation: Dowen, Jill M., and Richard A. Young. "SMC Complexes Link Gene Expression and Genome Architecture." Current Opinion in Genetics & Development 25 (April 2014): 131–137.

As Published: http://dx.doi.org/10.1016/j.gde.2013.11.009

Publisher: Elsevier

Persistent URL: http://hdl.handle.net/1721.1/103905

Version: Author's final manuscript: final author's manuscript post peer review, without publisher's formatting or copy editing

Terms of use: Creative Commons Attribution-NonCommercial-NoDerivs License

Massachusetts Institute of Technology

NIH Public Access
Author Manuscript
Curr Opin Genet Dev. Author manuscript; available in PMC 2015 May 08.

Published in final edited form as:
Curr Opin Genet Dev. 2014 April ; 0: 131–137. doi:10.1016/j.gde.2013.11.009.

SMC Complexes Link Gene Expression and Genome Architecture

Jill M. Dowen[1] and **Richard A. Young**[1,2]

[1]Whitehead Institute for Biomedical Research, 9 Cambridge Center, Cambridge, MA 02142

[2]Department of Biology, Massachusetts Institute of Technology, Cambridge, MA, 02139

Abstract

The Structural Maintenance of Chromosomes (SMC) complexes are associated with transcriptional enhancers, promoters and insulators, where they contribute to the control of gene expression and genome structure. We review here recent insights into the interlinked roles of SMC complexes in gene expression and genome architecture. Among these, we note evidence that SMC complexes play important roles in the regulation of genes that control cell identity. We conclude by reviewing diseases associated with SMC mutations.

SMC complexes

The Structural Maintenance of Chromosome (SMC) complexes are ring-shaped protein complexes that can link two DNA molecules (Figure 1) [1,2]. These complexes can accommodate two nucleosome-bound DNA molecules within the ring, although other mechanisms have been proposed for the ability of these complexes to link DNA [2–5]. SMC complexes are composed of two SMC subunits that act as long coiled-coil arms, a kleisin subunit that bridges the gap between the arms, and one or two heat repeat-containing subunits [1]. This general subunit composition is conserved from the single bacterial SMC complex through the various complexes found in vertebrates. Mammalian cells possess multiple SMC complexes with varied functions, which include mitotic cohesin, meiotic cohesin, condensin I, condensin II, and the SMC5/SMC6 DNA repair complex [6,7].

Bacteria possess a single SMC complex that functions in chromosome partitioning and proper nucleoid structure [8,9]. Eukaryotic SMC complexes were first shown to play important roles in chromosome maintenance during the cell cycle; cohesin maintains sister chromatid cohesion and condensin contributes to the compaction of chromosomes during mitosis [1,2,10,11]. Cohesin and condensin were later found to have roles in gene expression and interphase chromatin organization, which is the focus of this review.

© 2013 Elsevier Ltd. All rights reserved.

Corresponding Author: Richard A. Young, Whitehead Institute for Biomedical Research, 9 Cambridge Center, Cambridge, MA 02142, Tel: (617) 258-5218, Fax: (617) 258-0376, young@wi.mit.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

SMC-mediated control of gene expression

Early evidence that SMC complexes make functional contributions to gene regulation came from studies of gene expression and dosage compensation in yeast, *D. melanogaster* and *C. elegans* [12,13]. In yeast, cohesin was found to be involved in the silencing of heterochromatin [14,15]. Reduction of cohesin levels by as much as 80% caused defects in transcription, but had little effect on normal sister chromatid cohesion and chromosome segregation, suggesting that normal levels of cohesin are especially important for gene control [16,17]. In flies, the cohesin loading protein Nipped-B was found to contribute to gene activation [18] and disruption of cohesin was shown to affect expression of hundreds of genes, leading to developmental deficits [16,19,20]. Condensin mutations were found to alter the position effect variegation of reporter genes in *D. melanogaster* [21]. Dosage compensation in *C. elegans* was also found to be controlled by SMC complexes. The *C. elegans* Dosage Compensation Complex (DCC), which differs from the canonical condensin complex by a single subunit [22,23], was shown to be targeted to the two X chromosomes of hermaphrodites, where it caused a 50% reduction in transcription from genes on each of these chromosomes [24,25].

In vertebrates, cohesin, condensin I and condensin II have been shown to be associated with transcriptionally active enhancers and promoters and appear to contribute to stable enhancer-promoter DNA looping [26–31]. Among these SMC complexes, the genome-wide occupancy and function of cohesin is best studied, and these studies have led to the following model for gene activation. During transcription initiation, DNA-binding transcription factors bind to enhancer elements and recruit a variety of cofactors, including the Mediator coactivator, which in turn binds RNA polymerase II at promoter sites, forming an enhancer-promoter DNA loop (Figure 2) [32–35]. The SMC-loading factor NIPBL binds Mediator and loads cohesin at these sites [28,36]. The enhancer-promoter loops mediated by cohesin occur at genes important for cell identity [27,37]. Once loaded at promoters, the cohesin ring is able to translocate along DNA, possibly due to the action of transcribing RNA Polymerase [38,39]. A substantial fraction of cohesin is also associated with CTCF-bound regions of the genome [28,40], and this may be a consequence of NIPBL-dependent loading of cohesin at promoters followed by translocation to CTCF sites, or NIPBL-independent loading of cohesin at CTCF sites. Some of these cohesin-associated CTCF sites interact with regulatory elements and facilitate gene activation, while others are found at the boundary elements of topological domains, where they function as insulators, thus preventing the spread of an active transcriptional state beyond the boundary [40–53].

Vertebrates have two condensin complexes that associate sequentially with chromosomes during the cell cycle, show distinct patterns of binding to mitotic chromosomes and play different roles in chromosome architecture [54–57]. Condensin II is present in the nucleus throughout the cell cycle and is required for chromosome condensation during early prophase [55,57]. Condensin I, which is excluded from the nucleus during interphase, is loaded onto chromosomes during prometaphase, when it is required for complete removal of cohesin from chromosome arms, chromosome shortening and normal metaphase progression [55,57,58]. The condensins are thought to encircle DNA and act as a clamp during condensation, thereby providing structural integrity to segregating chromosomes [1,12,59–

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

61]. Low-resolution imaging suggests that condensin I and II occupy discrete domains that cover the length of mitotic chromosomes [55–57]. However, recent high-resolution ChIP-seq studies show that condensin I and II occupy the same regions of the genome with both complexes present at enhancers, promoters, centromeres and telomeres, and absent from heterochromatic regions [26,31]. Loading of the condensin complexes at actively transcribed genes depends, like cohesin, on the function of the SMC-loading factor NIPBL [26,62].

Regulation of SMC complexes at genes

Regulation of SMC loading and unloading at the enhancer-promoter interface is almost certainly a highly dynamic process, but is not yet well understood. Contact with the activation domains of transcription factors causes a modification in the structure of the Mediator complex that is thought to enhance NIPBL binding to Mediator, and this may be an underlying mechanism that regulates cohesin loading [63]. The functions of SMC complexes in sister chromatid cohesion can be regulated by phosphorylation, acetylation and sumoylation of their subunits, but it is not yet clear whether these modifications also play roles in gene regulation [64,65].

Cohesin removal is also important for normal gene expression [66]. Removal of SMC complexes from DNA is thought to occur through two different mechanisms, one that operates predominantly in chromosome arms and the other in centromeric DNA [67]. During the cell cycle, most cohesin molecules are removed from chromosome arms in prophase via the action of WAPL [66,68]. In WAPL-depleted cells, cohesin occupancy at transcription starts sites is altered and expression of many genes is changed [66]. Recent studies suggest that WAPL mediates a transient opening of the cohesin ring at the SMC3/kleisin interface [69–71]. The second mechanism of cohesin release occurs during anaphase when sister chromatid cohesion is lost and cohesin molecules are released from centromeres via proteolytic cleavage by Separase [72,73].

SMC complexes in control of cell identity

Super-enhancers are large clusters of transcriptional enhancers that drive expression of the key genes that control and define cell identity [26,27,74,75]. These domains are associated with genes encoding master transcription factors and other key proteins that play important roles in the biology of these cells. The importance of these domains is emphasized by the observation that sequence variation associated with a broad spectrum of diseases is especially enriched in the super-enhancers of disease-relevant cell types [27,76]. Super-enhancers contain unusually high levels of Mediator and SMC complexes; based on ChIP-seq reads, 20–40% of the Mediator, cohesin and condensin II protein associated with enhancers in murine embryonic stem cells is bound to the ~230 superenhancers [26,74]. Furthermore, knockdown of mediator, cohesin and condensin II causes a disproportionate loss of transcription of super-enhancer-associated genes [26,74]. These results indicate that transcriptional control of key cell identity genes is especially dependent on Mediator and SMC complexes.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

SMC contributions to chromosome structure

Chromosomes are organized into a hierarchy of structures, ranging from DNA loops such as enhancer-promoter loops, to topological domains that appear to average ~0.8 Mb, to chromosome compartments and territories [46,77–80]. The formation of enhancer-promoter DNA loops at active genes (Figure 2), as well as other loops involving CTCF, produce one level of chromosome organization that is facilitated by SMC complexes. As might be expected, such DNA loops are unique to cell state and change during differentiation and reprogramming [81–84]. These DNA loops are also thought to be dynamic within individual cells [77]. In contrast, topological domains are shared by the different cell types of an organism, conserved across species, and their boundaries contain insulators [46,85]. The expression of genes within a topological domain is generally correlated [77,86–88]. Since the boundaries of topological domains contain CTCF sites, and cohesin is found associated with such sites, it seems likely that cohesin contributes to the structure of topological domains. However, there are conflicting views on this subject, as one recent study detected few changes in topological domain organization upon loss of cohesin, while another study using a higher resolution analysis in a different cell type observed global changes in domain organization [89,90]. It is not yet clear whether the SMC complexes contribute to chromosome compartments, which consist of multiple topological domains, or chromosome territories, which consist of multiple chromosome compartments [77,91,92].

The condensin complexes are thought to contribute to chromosome compaction, which can be viewed as another level of chromosome organization [93–95]. Evidence in *D. melanogaster* and in mammalian cells suggest that SMC complexes are generally associated with transcriptionally active euchromatin and are present at much lower levels within heterochromatin [26,28,96,97]. This is consistent with evidence that these complexes are loaded on chromosome arms by the transcription initiation apparatus, and suggests that the mechanisms involved in gene repression in heterochromatin do not rely on SMC complexes.

SMC mutations and disease

Defects in cohesin and condensin can lead to genome disorganization, cell cycle delay, altered transcription and cell death [11,26,28,55–57,65,93,98–100]. Mutations in cohesin and its regulatory proteins cause a broad spectrum of developmental diseases termed cohesinopathies [101,102]. In Cornelia de Lange Syndrome, for example, patients have mutations in the cohesin subunits SMC1 and SMC3, as well as the SMC-loading factor NIPBL [103–105]. Mutations in the cohesin acetyltransferase ESCO2 can cause the related Roberts Syndrome [106,107]. Mutations in SMC proteins are also found in some cancers. Mutations in the cohesin subunit STAG2 frequently occur in a range of tumor types including urothelial bladder cancer and glioblastoma multiforme, while mutations in SMC3 are associated with acute myeloid leukemia and may contribute to its pathogenesis [108–112]. Mutations in two condensin subunits, SMC2 and SMC4, are found in pyothorax-associated lymphoma [113]. Condensin becomes overexpressed in Wnt-activated hyperplastic cells allowing for rapid proliferation [114]. It is likely that these cohesin and condensin defects result in the loss of long-range interactions between regulatory elements and their genes, leading to misregulation of cell type-specific gene expression programs.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Conclusions

The loading and unloading of SMC complexes at transcriptional regulatory elements links the control of gene expression to the control of chromosome structure. Proper expression of genes that control cell identity is especially dependent on the functions of SMC complexes, and mutations in the SMC complexes cause diseases associated with a loss of cell identity. Thus, improved understanding of the roles of SMC complexes in gene regulation, chromosome structure and cell identity should advance our understanding of the relationships between these important processes and the mechanisms involved in the cohesinopathies and cancer.

Acknowledgments

We thank Brian Abraham, Ashley Lau, Xiong Ji, and Heather Hoke for critical reading of the manuscript. This review was supported by the National Institutes of Health under Ruth L. Kirschstein National Research Service Award (CA168263-01A1) from the National Cancer Institute (JMD) and by NIH grant HG002668 (RY).

References and recommended reading

1. Hirano T. At the heart of the chromosome: SMC proteins in action. Nat Rev Mol Cell Biol. 2006; 7:311–322. [PubMed: 16633335]
2. Nasmyth K, Haering CH. The structure and function of SMC and kleisin complexes. Annu Rev Biochem. 2005; 74:595–648. [PubMed: 15952899]
3. Ivanov D, Nasmyth K. A topological interaction between cohesin rings and a circular minichromosome. Cell. 2005; 122:849–860. [PubMed: 16179255]
4. Haering CH, Farcas AM, Arumugam P, Metson J, Nasmyth K. The cohesin ring concatenates sister DNA molecules. Nature. 2008; 454:297–301. [PubMed: 18596691]
5. Nasmyth K, Haering CH. Cohesin: its roles and mechanisms. Annu Rev Genet. 2009; 43:525–558. [PubMed: 19886810]
6. Peters JM, Tedeschi A, Schmitz J. The cohesin complex and its roles in chromosome biology. Genes Dev. 2008; 22:3089–3114. [PubMed: 19056890]
7. Hirano T. SMC proteins and chromosome mechanics: from bacteria to humans. Philos Trans R Soc Lond B Biol Sci. 2005; 360:507–514. [PubMed: 15897176]
8. Moriya S, Tsujikawa E, Hassan AK, Asai K, Kodama T, Ogasawara N. A Bacillus subtilis gene-encoding protein homologous to eukaryotic SMC motor protein is necessary for chromosome partition. Mol Microbiol. 1998; 29:179–187. [PubMed: 9701812]
9. Britton RA, Lin DC, Grossman AD. Characterization of a prokaryotic SMC protein involved in chromosome partitioning. Genes Dev. 1998; 12:1254–1259. [PubMed: 9573042]
10. Hudson DF, Marshall KM, Earnshaw WC. Condensin: Architect of mitotic chromosomes. Chromosome Res. 2009; 17:131–144. [PubMed: 19308696]
11. Hirano T. Condensins: universal organizers of chromosomes with diverse functions. Genes Dev. 2012; 26:1659–1678. [PubMed: 22855829]
12. Wood AJ, Severson AF, Meyer BJ. Condensin and cohesin complexity: the expanding repertoire of functions. Nat Rev Genet. 2010; 11:391–404. [PubMed: 20442714]
13. Dorsett D. Cohesin: genomic insights into controlling gene transcription and development. Curr Opin Genet Dev. 2011; 21:199–206. [PubMed: 21324671]
14. Dheur S, Saupe SJ, Genier S, Vazquez S, Javerzat JP. Role for cohesin in the formation of a heterochromatic domain at fission yeast subtelomeres. Mol Cell Biol. 2011; 31:1088–1097. [PubMed: 21189291]
15. Donze D, Adams CR, Rine J, Kamakaka RT. The boundaries of the silenced HMR domain in Saccharomyces cerevisiae. Genes Dev. 1999; 13:698–708. [PubMed: 10090726]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

16. Schaaf CA, Misulovin Z, Sahota G, Siddiqui AM, Schwartz YB, Kahn TG, Pirrotta V, Gause M, Dorsett D. Regulation of the Drosophila Enhancer of split and invected-engrailed gene complexes by sister chromatid cohesion proteins. PLoS One. 2009; 4:e6202. [PubMed: 19587787]

17. Heidinger-Pauli JM, Mert O, Davenport C, Guacci V, Koshland D. Systematic reduction of cohesin differentially affects chromosome segregation, condensation, and DNA repair. Curr Biol. 2010; 20:957–963. [PubMed: 20451387]

18. Rollins RA, Morcillo P, Dorsett D. Nipped-B, a Drosophila homologue of chromosomal adherins, participates in activation by remote enhancers in the cut and Ultrabithorax genes. Genetics. 1999; 152:577–593. [PubMed: 10353901]

19. Rollins RA, Korom M, Aulner N, Martens A, Dorsett D. Drosophila nipped-B protein supports sister chromatid cohesion and opposes the stromalin/Scc3 cohesion factor to facilitate long-range activation of the cut gene. Mol Cell Biol. 2004; 24:3100–3111. [PubMed: 15060134]

20. Dorsett D, Eissenberg JC, Misulovin Z, Martens A, Redding B, McKim K. Effects of sister chromatid cohesion proteins on cut gene expression during wing development in Drosophila. Development. 2005; 132:4743–4753. [PubMed: 16207752]

21. Cobbe N, Savvidou E, Heck MM. Diverse mitotic and interphase functions of condensins in Drosophila. Genetics. 2006; 172:991–1008. [PubMed: 16272408]

22. Csankovszki G, Collette K, Spahl K, Carey J, Snyder M, Petty E, Patel U, Tabuchi T, Liu H, McLeod I, et al. Three distinct condensin complexes control C. elegans chromosome dynamics. Curr Biol. 2009; 19:9–19. [PubMed: 19119011]

23. Jans J, Gladden JM, Ralston EJ, Pickle CS, Michel AH, Pferdehirt RR, Eisen MB, Meyer BJ. A condensin-like dosage compensation complex acts at a distance to control expression throughout the genome. Genes Dev. 2009; 23:602–618. [PubMed: 19270160]

24. Ercan S, Lieb JD: C. elegans dosage compensation: a window into mechanisms of domain-scale gene regulation. Chromosome Res. 2009; 17:215–227. [PubMed: 19308702]

25. Meyer BJ. Targeting X chromosomes for repression. Curr Opin Genet Dev. 2010; 20:179–189. [PubMed: 20381335]

26. Dowen JM, Bilodeau S, Orlando DA, Hubner MR, Abraham BJ, Spector DL, Young RA. Multiple Structural Maintenance of Chromosome Complexes at Transcriptional Regulatory Elements. Stem Cell Reports. 2013 In Press. . * This paper shows that the mammalian Condensin II complex occupies enhancers, super-enhancers and promoters of active genes in murine embryonic stem cells. This work also shows that Condensin II is loaded onto chromosomes during interphase by NIPBL, similar to the Cohesin complex.

27. Hnisz D, Abraham BJ, Lee TI, Lau A, Saint-Andre V, Sigova AA, Hoke HA, Young RA. Transcriptional super-enhancers connected to cell identity and disease. Cell. 2013 In Press.

28. Kagey MH, Newman JJ, Bilodeau S, Zhan Y, Orlando DA, van Berkum NL, Ebmeier CC, Goossens J, Rahl PB, Levine SS, et al. Mediator and cohesin connect gene expression and chromatin architecture. Nature. 2010; 467:430–435. [PubMed: 20720539]

29. Schmidt D, Schwalie PC, Ross-Innes CS, Hurtado A, Brown GD, Carroll JS, Flicek P, Odom DT. A CTCF-independent role for cohesin in tissuespecific transcription. Genome Res. 2010; 20:578–588. [PubMed: 20219941]

30. Seitan VC, Merkenschlager M. Cohesin and chromatin organisation. Curr Opin Genet Dev. 2012; 22:93–100. [PubMed: 22155130]

31. Kim JH, Zhang T, Wong NC, Davidson N, Maksimovic J, Oshlack A, Earnshaw WC, Kalitsis P, Hudson DF. Condensin I associates with structural and gene regulatory regions in vertebrate chromosomes. Nat Commun. 2013; 4:2537. [PubMed: 24088984] . * In this paper the authors show that the vertebrate Condensin I complex occupies the promoters of active genes, centromeres and telomeres during mitosis. Condensin I knockout cells show decreased expression of genes during G1 suggesting that Condensin I may participate in transcriptional memory.

32. Lee TI, Young RA. Transcriptional regulation and its misregulation in disease. Cell. 2013; 152:1237–1251. [PubMed: 23498934]

33. Roeder RG. Transcriptional regulation and the role of diverse coactivators in animal cells. FEBS Lett. 2005; 579:909–915. [PubMed: 15680973]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

34. Lelli KM, Slattery M, Mann RS. Disentangling the many layers of eukaryotic transcriptional regulation. Annu Rev Genet. 2012; 46:43–68. [PubMed: 22934649]
35. Spitz F, Furlong EE. Transcription factors: from enhancer binding to developmental control. Nat Rev Genet. 2012; 13:613–626. [PubMed: 22868264]
36. Ciosk R, Shirayama M, Shevchenko A, Tanaka T, Toth A, Nasmyth K. Cohesin's binding to chromosomes depends on a separate complex consisting of Scc2 and Scc4 proteins. Mol Cell. 2000; 5:243–254. [PubMed: 10882066]
37. Lin C, Garruss AS, Luo Z, Guo F, Shilatifard A. The RNA Pol II elongation factor Ell3 marks enhancers in ES cells and primes future gene activation. Cell. 2013; 152:144–156. [PubMed: 23273992] . * This study found that elongation factor Ell3 occupies enhancers in mESCs and is important for regulating Pol2 occupancy at the promoters of associated genes. Communication between Ell3-bound enhancers and promoters requires Cohesin and Ell3 occupancy appears to predict future gene activation.
38. Lengronne A, Katou Y, Mori S, Yokobayashi S, Kelly GP, Itoh T, Watanabe Y, Shirahige K, Uhlmann F. Cohesin relocation from sites of chromosomal loading to places of convergent transcription. Nature. 2004; 430:573–578. [PubMed: 15229615]
39. Ocampo-Hafalla MT, Uhlmann F. Cohesin loading and sliding. J Cell Sci. 2011; 124:685–691. [PubMed: 21321326]
40. Wendt KS, Yoshida K, Itoh T, Bando M, Koch B, Schirghuber E, Tsutsumi S, Nagae G, Ishihara K, Mishiro T, et al. Cohesin mediates transcriptional insulation by CCCTC-binding factor. Nature. 2008; 451:796–801. [PubMed: 18235444]
41. Lee BK, Iyer VR. Genome-wide studies of CCCTC-binding factor (CTCF) and cohesin provide insight into chromatin structure and regulation. J Biol Chem. 2012; 287:30906–30913. [PubMed: 22952237]
42. Phillips-Cremins JE, Corces VG. Chromatin insulators: linking genome organization to cellular function. Mol Cell. 2013; 50:461–474. [PubMed: 23706817]
43. Merkenschlager M, Odom DT. CTCF and cohesin: linking gene regulatory elements with their targets. Cell. 2013; 152:1285–1297. [PubMed: 23498937]
44. Phillips JE, Corces VG. CTCF: master weaver of the genome. Cell. 2009; 137:1194–1211. [PubMed: 19563753]
45. Parelho V, Hadjur S, Spivakov M, Leleu M, Sauer S, Gregson HC, Jarmuz A, Canzonetta C, Webster Z, Nesterova T, et al. Cohesins functionally associate with CTCF on mammalian chromosome arms. Cell. 2008; 132:422–433. [PubMed: 18237772]
46. Dixon JR, Selvaraj S, Yue F, Kim A, Li Y, Shen Y, Hu M, Liu JS, Ren B. Topological domains in mammalian genomes identified by analysis of chromatin interactions. Nature. 2012; 485:376–380. [PubMed: 22495300] . ** This important study shows that mammalian genomes are organized into roughly 200 topological domains. These domains, which are conserved across cell types and species, have classical insulator sites at their boundaries.
47. Cuddapah S, Jothi R, Schones DE, Roh TY, Cui K, Zhao K. Global analysis of the insulator binding protein CTCF in chromatin barrier regions reveals demarcation of active and repressive domains. Genome Res. 2009; 19:24–32. [PubMed: 19056695]
48. Horsfield JA, Anagnostou SH, Hu JK, Cho KH, Geisler R, Lieschke G, Crosier KE, Crosier PS. Cohesin-dependent regulation of Runx genes. Development. 2007; 134:2639–2649. [PubMed: 17567667]
49. Hou C, Dale R, Dean A. Cell type specificity of chromatin organization mediated by CTCF and cohesin. Proc Natl Acad Sci U S A. 2010; 107:3651–3656. [PubMed: 20133600]
50. Mishiro T, Ishihara K, Hino S, Tsutsumi S, Aburatani H, Shirahige K, Kinoshita Y, Nakao M. Architectural roles of multiple chromatin insulators at the human apolipoprotein gene cluster. EMBO J. 2009; 28:1234–1245. [PubMed: 19322193]
51. Nativio R, Wendt KS, Ito Y, Huddleston JE, Uribe-Lewis S, Woodfine K, Krueger C, Reik W, Peters JM, Murrell A. Cohesin is required for higherorder chromatin conformation at the imprinted IGF2-H19 locus. PLoS Genet. 2009; 5:e1000739. [PubMed: 19956766]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

52. Rubio ED, Reiss DJ, Welcsh PL, Disteche CM, Filippova GN, Baliga NS, Aebersold R, Ranish JA, Krumm A. CTCF physically links cohesin to chromatin. Proc Natl Acad Sci U S A. 2008; 105:8309–8314. [PubMed: 18550811]
53. Stedman W, Kang H, Lin S, Kissil JL, Bartolomei MS, Lieberman PM. Cohesins localize with CTCF at the KSHV latency control region and at cellular c-myc and H19/Igf2 insulators. EMBO J. 2008; 27:654–666. [PubMed: 18219272]
54. Shintomi K, Hirano T. The relative ratio of condensin I to II determines chromosome shapes. Genes Dev. 2011
55. Ono T, Fang Y, Spector DL, Hirano T. Spatial and temporal regulation of Condensins I and II in mitotic chromosome assembly in human cells. Mol Biol Cell. 2004; 15:3296–3308. [PubMed: 15146063]
56. Ono T, Losada A, Hirano M, Myers MP, Neuwald AF, Hirano T. Differential contributions of condensin I and condensin II to mitotic chromosome architecture in vertebrate cells. Cell. 2003; 115:109–121. [PubMed: 14532007]
57. Hirota T, Gerlich D, Koch B, Ellenberg J, Peters JM. Distinct functions of condensin I and II in mitotic chromosome assembly. J Cell Sci. 2004; 117:6435–6445. [PubMed: 15572404]
58. Yu HG, Koshland D. Chromosome morphogenesis: condensindependent cohesin removal during meiosis. Cell. 2005; 123:397–407. [PubMed: 16269332]
59. Cuylen S, Metz J, Haering CH. Condensin structures chromosomal DNA through topological links. Nat Struct Mol Biol. 2011. * This paper shows that Condensin complexes encircle DNA in a manner similar to Cohesin. The authors found that cleavage of DNA and ring opening both caused Condensin to be released from minichromosomes, and Condensin ring integrity is important for proper segregation of chromsome arms.
60. Cuylen S, Haering CH. Deciphering condensin action during chromosome segregation. Trends Cell Biol. 2011
61. McNairn AJ, Gerton JL. The chromosome glue gets a little stickier. Trends Genet. 2008; 24:382–389. [PubMed: 18602182]
62. D'Ambrosio C, Schmidt CK, Katou Y, Kelly G, Itoh T, Shirahige K, Uhlmann F. Identification of cis-acting sites for condensin loading onto budding yeast chromosomes. Genes Dev. 2008; 22:2215–2227. [PubMed: 18708580]
63. Ebmeier CC, Taatjes DJ. Activator-Mediator binding regulates Mediatorcofactor interactions. Proc Natl Acad Sci U S A. 2010
64. Piazza I, Haering CH, Rutkowska A. Condensin: crafting the chromosome landscape. Chromosoma. 2013; 122:175–190. [PubMed: 23546018]
65. Dorsett D, Strom L. The ancient and evolving roles of cohesin in gene expression and DNA repair. Curr Biol. 2012; 22:R240–R250. [PubMed: 22497943]
66. Tedeschi A, Wutz G, Huet S, Jaritz M, Wuensche A, Schirghuber E, Davidson IF, Tang W, Cisneros DA, Bhaskara V, et al. Wapl is an essential regulator of chromatin structure and chromosome segregation. Nature. 2013
67. Nasmyth K. Cohesin: a catenase with separate entry and exit gates? Nat Cell Biol. 2011; 13:1170–1177. [PubMed: 21968990]
68. Nishiyama T, Sykora MM, 't Velda PJHI, Mechtler K, Peters JM. Aurora B and Cdk1 mediate Wapl activation and release of acetylated cohesin from chromosomes by phosphorylating Sororin. Proceedings of the National Academy of Sciences of the United States of America. 2013; 110:13404–13409. [PubMed: 23901111]
69. Chan KL, Roig MB, Hu B, Beckouet F, Metson J, Nasmyth K. Cohesin's DNA exit gate is distinct from its entrance gate and is regulated by acetylation. Cell. 2012; 150:961–974. [PubMed: 22901742] . * This paper dissects the elusive molecular mechanism of Cohesin's removal from chromosome arms. They find ring opening occurrs at the interface between Smc3 and alpha-klesin subunits and that acetylation of Smc3 counteracts the WAPL-mediated dissociation of Cohesin.
70. Eichinger CS, Kurze A, Oliveira RA, Nasmyth K. Disengaging the Smc3/kleisin interface releases cohesin from Drosophila chromosomes during interphase and mitosis. EMBO J. 2013; 32:656–665. [PubMed: 23340528]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

71. Buheitel J, Stemmann O. Prophase pathway-dependent removal of cohesin from human chromosomes requires opening of the Smc3- Scc1 gate. EMBO J. 2013; 32:666–676. [PubMed: 23361318]

72. Uhlmann F, Wernic D, Poupart MA, Koonin EV, Nasmyth K. Cleavage of cohesin by the CD clan protease separin triggers anaphase in yeast. Cell. 2000; 103:375–386. [PubMed: 11081625]

73. Hauf S, Waizenegger IC, Peters JM. Cohesin cleavage by separase required for anaphase and cytokinesis in human cells. Science. 2001; 293:1320–1323. [PubMed: 11509732]

74. Whyte WA, Orlando DA, Hnisz D, Abraham BJ, Lin CY, Kagey MH, Rahl PB, Lee TI, Young RA. Master transcription factors and mediator establish super-enhancers at key cell identity genes. Cell. 2013; 153:307–319. [PubMed: 23582322]

75. Loven J, Hoke HA, Lin CY, Lau A, Orlando DA, Vakoc CR, Bradner JE, Lee TI, Young RA. Selective inhibition of tumor oncogenes by disruption of super-enhancers. Cell. 2013; 153:320–334. [PubMed: 23582323]

76. Parker SC, Stitzel ML, Taylor DL, Orozco JM, Erdos MR, Akiyama JA, van Bueren KL, Chines PS, Narisu N, Program NCS, et al. Chromatin stretch enhancer states drive cell-specific gene regulation and harbor human disease risk variants. Proc Natl Acad Sci U S A. 2013

77. Gibcus JH, Dekker J. The hierarchy of the 3D genome. Mol Cell. 2013; 49:773–782. [PubMed: 23473598] . ** This work describes the layers of organization within the eukaryotic genome. It unifies a variety of results obtained with different experimental techniques and systems to provide an overarching view of how the organization of the genome is linked to its regulation.

78. Hubner MR, Eckersley-Maslin MA, Spector DL. Chromatin organization and transcriptional regulation. Curr Opin Genet Dev. 2013; 23:89–95. [PubMed: 23270812]

79. Lieberman-Aiden E, van Berkum NL, Williams L, Imakaev M, Ragoczy T, Telling A, Amit I, Lajoie BR, Sabo PJ, Dorschner MO, et al. Comprehensive mapping of long-range interactions reveals folding principles of the human genome. Science. 2009; 326:289–293. [PubMed: 19815776]

80. Tanay A, Cavalli G. Chromosomal domains: epigenetic contexts and functional implications of genomic compartmentalization. Curr Opin Genet Dev. 2013; 23:197–203. [PubMed: 23414654]

81. Nora EP, Lajoie BR, Schulz EG, Giorgetti L, Okamoto I, Servant N, Piolot T, van Berkum NL, Meisig J, Sedat J, et al. Spatial partitioning of the regulatory landscape of the X-inactivation centre. Nature. 2012; 485:381–385. [PubMed: 22495304]

82. Apostolou E, Ferrari F, Walsh RM, Bar-Nur O, Stadtfeld M, Cheloufi S, Stuart HT, Polo JM, Ohsumi TK, Borowsky ML, et al. Genome-wide chromatin interactions of the Nanog locus in pluripotency, differentiation, and reprogramming. Cell Stem Cell. 2013; 12:699–712. [PubMed: 23665121] . * This study focuses on the chromatin interactions involving the Nanog locus in embryonic stem cells and how they change during reprogramming and differentiation. The authors show that Mediator and Cohesin facilitate these interactions and are important for maintenance of the pluripotent state.

83. Wei Z, Gao F, Kim S, Yang H, Lyu J, An W, Wang K, Lu W. Klf4 organizes long-range chromosomal interactions with the oct4 locus in reprogramming and pluripotency. Cell Stem Cell. 2013; 13:36–47. [PubMed: 23747203]

84. Demare LE, Leng J, Cotney J, Reilly SK, Yin J, Sarro R, Noonan JP. The genomic landscape of cohesin-associated chromatin interactions. Genome Res. 2013; 23:1224–1234. [PubMed: 23704192] . * This paper used ChIA-PET to identify Cohesin-mediated chromatin interactions across the genome. The authors demonstrate that the pattern of loops varies between embryonic limb bud and cortex according to their gene expression programs.

85. Smallwood A, Ren B. Genome organization and long-range regulation of gene expression by enhancers. Curr Opin Cell Biol. 2013; 25:387–394. [PubMed: 23465541]

86. Caron H, van Schaik B, van der Mee M, Baas F, Riggins G, van Sluis P, Hermus MC, van Asperen R, Boon K, Voute PA, et al. The human transcriptome map: clustering of highly expressed genes in chromosomal domains. Science. 2001; 291:1289–1292. [PubMed: 11181992]

87. Cavalli G, Misteli T. Functional implications of genome topology. Nat Struct Mol Biol. 2013; 20:290–299. [PubMed: 23463314]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

88. Gierman HJ, Indemans MH, Koster J, Goetze S, Seppen J, Geerts D, van Driel R, Versteeg R. Domain-wide regulation of gene expression in the human genome. Genome Res. 2007; 17:1286–1295. [PubMed: 17693573]

89. Seitan V, Faure A, Zhan Y, McCord R, Lajoie B, Ing-Simmons E, Lenhard B, Giorgetti L, Heard E, Fisher A, et al. Cohesin-based chromatin interactions enable regulated gene expression within pre-existing architectural compartments. Genome Res. 2013

90. Sofueva S, Yaffe E, Chan WC, Georgopoulou D, Vietri Rudan M, Mira- Bontenbal H, Pollard SM, Schroth GP, Tanay A, Hadjur S. Cohesinmediated interactions organize chromosomal domain architecture. EMBO J. 2013. * This work highlights a role for Cohesin in the organization of topological domains in astrocytes. Upon reduced Cohesin levels, the frequency of interactions within topological domains is reduced while the frequency of interactions between topological domains is increased.

91. Nagano T, Lubling Y, Stevens TJ, Schoenfelder S, Yaffe E, Dean W, Laue ED, Tanay A, Fraser P. Single-cell Hi-C reveals cell-to-cell variability in chromosome structure. Nature. 2013

92. Krijger PH, de Laat W. Identical cells with different 3D genomes; cause and consequences? Curr Opin Genet Dev. 2013; 23:191–196. [PubMed: 23415810]

93. Fazzio TG, Panning B. Condensin complexes regulate mitotic progression and interphase chromatin structure in embryonic stem cells. J Cell Biol. 2010; 188:491–503. [PubMed: 20176923]

94. Bauer CR, Hartl TA, Bosco G. Condensin II promotes the formation of chromosome territories by inducing axial compaction of polyploid interphase chromosomes. PLoS Genet. 2012; 8:e1002873. [PubMed: 22956908]

95. Smith HF, Roberts MA, Nguyen HQ, Peterson M, Hartl TA, Wang XJ, Klebba JE, Rogers GC, Bosco G. Maintenance of interphase chromosome compaction and homolog pairing in Drosophila is regulated by the condensin cap-h2 and its partner mrg15. Genetics. 2013; 195:127–146. [PubMed: 23821596] . * In this paper the authors show that Mrg15 and Condensin interact and contribute to the control of chromosome structure. The cooperation of these proteins is integral to interphase genome organization, maintenance of chromosome length, axial compaction, and unpairing of polytene chromosomes.

96. Dorsett D. Cohesin, gene expression and development: lessons from Drosophila. Chromosome Res. 2009; 17:185–200. [PubMed: 19308700]

97. Longworth MS, Herr A, Ji JY, Dyson NJ. RBF1 promotes chromatin condensation through a conserved interaction with the Condensin II protein dCAP-D3. Genes Dev. 2008; 22:1011–1024. [PubMed: 18367646]

98. Jessberger R. The many functions of SMC proteins in chromosome dynamics. Nat Rev Mol Cell Biol. 2002; 3:767–778. [PubMed: 12360193]

99. Wendt KS, Peters JM. How cohesin and CTCF cooperate in regulating gene expression. Chromosome Res. 2009; 17:201–214. [PubMed: 19308701]

100. Hu G, Kim J, Xu Q, Leng Y, Orkin SH, Elledge SJ. A genome-wide RNAi screen identifies a new transcriptional module required for selfrenewal. Genes Dev. 2009; 23:837–848. [PubMed: 19339689]

101. Strachan T. Cornelia de Lange Syndrome and the link between chromosomal function, DNA repair and developmental gene regulation. Curr Opin Genet Dev. 2005; 15:258–264. [PubMed: 15917200]

102. Liu J, Krantz ID. Cohesin and human disease. Annu Rev Genomics Hum Genet. 2008; 9:303–320. [PubMed: 18767966]

103. Krantz ID, McCallum J, DeScipio C, Kaur M, Gillis LA, Yaeger D, Jukofsky L, Wasserman N, Bottani A, Morris CA, et al. Cornelia de Lange syndrome is caused by mutations in NIPBL, the human homolog of Drosophila melanogaster Nipped-B. Nat Genet. 2004; 36:631–635. [PubMed: 15146186]

104. Horsfield JA, Print CG, Monnich M. Diverse developmental disorders from the one ring: distinct molecular pathways underlie the cohesinopathies. Front Genet. 2012; 3:171. [PubMed: 22988450]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

105. Tonkin ET, Wang TJ, Lisgo S, Bamshad MJ, Strachan T. NIPBL, encoding a homolog of fungal Scc2-type sister chromatid cohesion proteins and fly Nipped-B, is mutated in Cornelia de Lange syndrome. Nat Genet. 2004; 36:636–641. [PubMed: 15146185]

106. Vega H, Waisfisz Q, Gordillo M, Sakai N, Yanagihara I, Yamada M, van Gosliga D, Kayserili H, Xu C, Ozono K, et al. Roberts syndrome is caused by mutations in ESCO2, a human homolog of yeast ECO1 that is essential for the establishment of sister chromatid cohesion. Nat Genet. 2005; 37:468–470. [PubMed: 15821733]

107. Schule B, Oviedo A, Johnston K, Pai S, Francke U. Inactivating mutations in ESCO2 cause SC phocomelia and Roberts syndrome: no phenotype-genotype correlation. Am J Hum Genet. 2005; 77:1117–1128. [PubMed: 16380922]

108. Solomon DA, Kim JS, Bondaruk J, Shariat SF, Wang ZF, Elkahloun AG, Ozawa T, Gerard J, Zhuang D, Zhang S, et al. Frequent truncating mutations of STAG2 in bladder cancer. Nat Genet. 2013

109. Balbas-Martinez C, Sagrera A, Carrillo-de-Santa-Pau E, Earl J, Marquez M, Vazquez M, Lapi E, Castro-Giner F, Beltran S, Bayes M, et al. Recurrent inactivation of STAG2 in bladder cancer is not associated with aneuploidy. Nat Genet. 2013

110. Aerts S, Cools J. Cancer: Mutations close in on gene regulation. Nature. 2013; 499:35–36. [PubMed: 23823789]

111. Ley TJ, Miller C, Ding L, Raphael BJ, Mungall AJ, Robertson AG, Hoadley K, Triche TJ, Laird PW, Baty JD, et al. Genomic and Epigenomic Landscapes of Adult De Novo Acute Myeloid Leukemia. New England Journal of Medicine. 2013; 368:2059–2074. [PubMed: 23634996]

112. Solomon DA, Kim T, Diaz-Martinez LA, Fair J, Elkahloun AG, Harris BT, Toretsky JA, Rosenberg SA, Shukla N, Ladanyi M, et al. Mutational inactivation of STAG2 causes aneuploidy in human cancer. Science. 2011; 333:1039–1043. [PubMed: 21852505]

113. Ham MF, Takakuwa T, Rahadiani N, Tresnasari K, Nakajima H, Aozasa K. Condensin mutations and abnormal chromosomal structures in pyothorax-associated lymphoma. Cancer Sci. 2007; 98:1041–1047. [PubMed: 17488335]

114. Davalos V, Suarez-Lopez L, Castano J, Messent A, Abasolo I, Fernandez Y, Guerra-Moreno A, Espin E, Armengol M, Musulen E, et al. Human SMC2 protein, a core subunit of human condensin complex, is a novel transcriptional target of the WNT signaling pathway and a new therapeutic target. J Biol Chem. 2012; 287:43472–43481. [PubMed: 23095742]

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

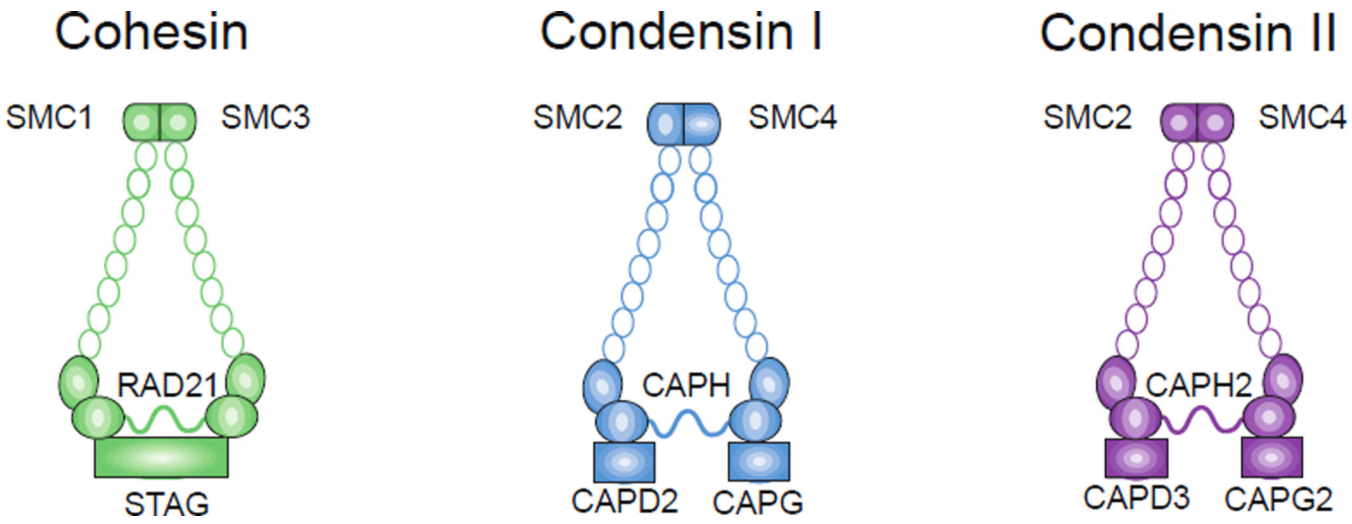

Figure 1.
Subunit composition of the mammalian SMC complexes cohesin, condensin I and condensin II.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

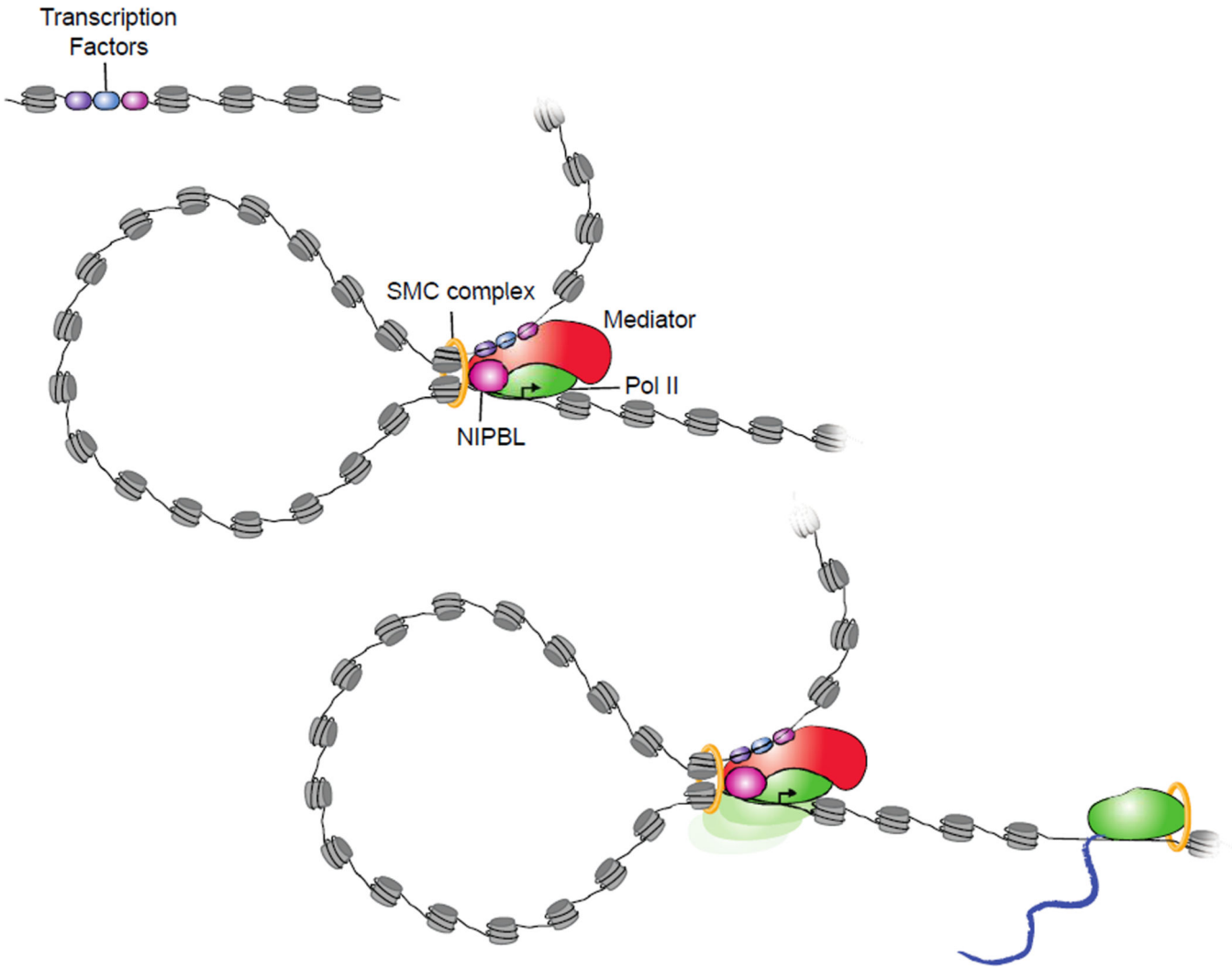

Figure 2.

Model for loading and translocation of SMC complexes during transcription. Transcription factors bind to enhancers and recruit the Mediator coactivator, NIPBL, and RNA Polymerase. NIPBL loads the SMC complexes at these regulatory elements where they contribute to the formation or stability of the enhancer-promoter DNA loop. Transcription elongation may facilitate translocation of SMC complexes to other regions of the chromosome.