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Cohesin in development and disease

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Summary

Cohesin is a ring-shaped complex, conserved from yeast to human, that was named for its ability to mediate sister chromatid cohesion. This function is essential for chromosome segregation in both mitosis and meiosis, and also for DNA repair. In addition, more recent studies have shown that cohesin influences gene expression during development through mechanisms that likely involve DNA looping and interactions with several transcriptional regulators. Here, we provide an overview of how cohesin functions, highlighting its role both in development and in disease.

Key words: Chromatin loops, Cohesion, Cohesinopathies

Introduction

The development of a complex multicellular organism from the fusion of two haploid cells requires two fundamental processes: one is cell proliferation, in order to grow; the other is cell differentiation, in order to generate specialized cells for tissues and organs. The cohesin complex plays key roles in both these processes. Cohesin was originally identified as the mediator of sister chromatid cohesion. It establishes a physical link between the two sister chromatids from the moment they arise from the replication fork. This link is essential for efficient DNA repair by homologous recombination during S/G2, and for proper chromosome alignment and segregation in mitosis. In this way, cohesin ensures the accurate transmission of genetic material during cell proliferation. Regarding cell differentiation, it is clear that what defines a cell type is not its genome, but how this genome is used. Increasing evidence supports the importance of higher order chromatin structure in the temporal and spatial regulation of transcription. We are only beginning to understand how the spatial organization of chromatin affects gene expression, but cohesin is emerging as an important contributor to such organization. Here, and in the accompanying poster, we briefly review our current knowledge of cohesin and its different functions, and focus on how these functions contribute to embryonic development.

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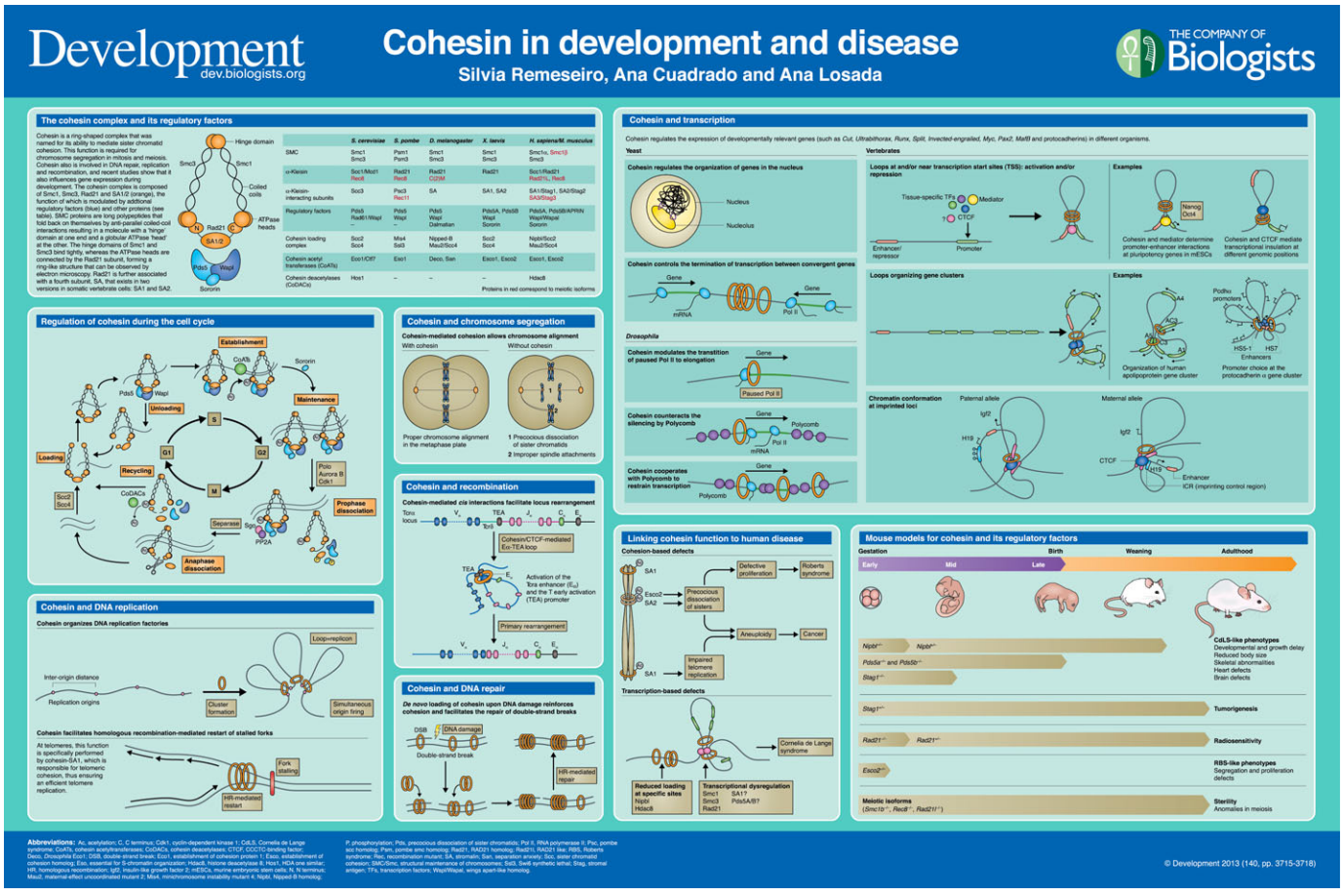

(See poster insert)

The cohesin complex

Cohesin consists of four subunits – Smc1, Smc3, Scc1/Rad21 and Scc3/SA – arranged in a ring-shaped structure. Smc1 and Smc3 belong to the structural maintenance of chromosomes (SMC) family of chromosomal ATPases that also includes the core subunits of condensin and of the Smc5/6 complex. These complexes are conserved from yeast to human, and SMC-like proteins contribute to chromosome organization and dynamics in bacteria and archaea (Hirano, 2005). Scc1/Rad21 belongs to the kleisin protein family and interacts with both Smc1 and Smc3 to close the ring. The Scc3/SA subunit in somatic vertebrate cells can be either SA1 or SA2, although additional variants for SA and other subunits also exist in meiotic cells.

The regulation of cohesin during the cell cycle

Cohesin topologically embraces chromatin fiber(s) within its ring-shaped structure (Nasmyth, 2011). The complex is recruited to chromatin during G1 in a process that requires the cohesin-interacting Scc2-Scc4 heterodimer (Nipbl-Mau2 in human cells) and ATP hydrolysis. This binding is quite dynamic; two proteins known as Pds5 (precocious dissociation of sister chromatids 5) and Wapl (wings apart-like homolog) associate with cohesin on chromatin and promote its unloading (Gerlich et al., 2006). The establishment of cohesion (i.e. entrapment of both sister chromatids) occurs during S phase. At this time, the cohesin Smc3 subunit is acetylated on two lysine residues by cohesin acetyltransferases (CoATs) (Rolef Ben-Shahar et al., 2008). This modification may trigger a conformational change in the cohesin complex that neutralizes the unloading action of Pds5-Wapl (Chan et al., 2012). In vertebrates, the establishment of cohesion also requires the binding of sororin to cohesin, which occurs through Pds5 (Nishiyama et al., 2010). At the onset of mitosis, as chromosome condense, most cohesin dissociates from chromatin. This prophase dissociation, which happens only in higher eukaryotes, is driven by Pds5-Wapl and requires phosphorylation of cohesin (Shintomi and Hirano, 2010). However, a small fraction of cohesin is protected from dissociation by Shugoshin-PP2A (protein phosphatase 2A) and remains bound to chromatin, mostly at pericentromeric regions. This population opposes the pulling forces of the spindle and allows chromosome alignment. At the onset of anaphase, activation of the anaphase-promoting complex APC/C drives the degradation of securin, so that separase can cleave the Rad21 subunit of chromatin-bound cohesin and dissolve cohesion. Cohesin deacetylases (CoDACs) allow cohesin complexes released during mitosis to be recycled and used in the ensuing G1 (reviewed by Remeseiro and Losada, 2013).

General mechanisms of cohesin action

In order to mediate cohesion, cohesin embraces two DNA segments (i.e. the two sister chromatids) *in trans*. During the S and G2 phases, this function is important for restarting of replication forks that become stalled at regions difficult to replicate (e.g. the telomeres) and repairing double-strand breaks by homologous recombination (Remeseiro et al., 2012a). During cell division, cohesion prevents the premature separation of sister chromatids under the pulling forces of spindle microtubules (Toyoda and Yanagida, 2006) and also facilitates bipolar attachment of the sister kinetochores. However, it has been postulated that cohesin may also entrap two distant DNA segments *in cis* to form a loop. Chromatin loops stabilized by cohesin can be of very different sizes and serve many purposes in interphase chromatin. For example, they organize replication factories to promote efficient origin firing (Guillou et al., 2010). They also facilitate Tcrα locus rearrangement, which is essential for T-cell differentiation (Seitan et al., 2011; Shih et al., 2012), and mediate the compaction of the Igh locus, which probably facilitates V(D)J recombination (Degner et al., 2011). Furthermore, they allow communication between gene promoters and their (distant) *cis*-regulatory regions (Kagey et al., 2010), and they can also isolate a genomic region to ensure its independent function and regulation. Although chromatin loops cannot be visualized by current microscopy techniques, their existence is revealed by the detection of physical interactions between distant genomic loci by means of chromosome conformation capture-derived technologies (de Wit and de Laat, 2012) and has also been inferred by fluorescent *in situ* hybridization-based approaches (Jhunjhunwala et al., 2008).

Cohesin and transcription

In yeast, cohesin contributes to gene regulation by defining the position of genes within the nucleus, i.e. their proximity to the nucleolus or to tDNA clusters (Gard et al., 2009). Overall, the complex is excluded from actively transcribed genes and accumulates at sites of convergent transcription (Ocampo-Hafalla and Uhlmann, 2011). In *S. pombe*, it also acts as a terminator of transcription (Gullerova and Proudfoot, 2008). However, in *Drosophila*, cohesin binds preferentially to active genes where it colocalizes with its loader and with RNA polymerase II (Misulovin et al., 2008). Elegant experiments in *Drosophila* salivary glands demonstrate that cohesin affects gene expression independently of its role as a mediator of sister chromatid cohesion (Pauli et al., 2010). Other experiments show that cohesin and its loader have dose-sensitive effects on the functions of genes involved in key developmental pathways (Dorsett, 2009). More recently, it was shown that cohesin can counteract silencing by Polycomb proteins, although in some cases it can cooperate with Polycomb to restrain transcription (Cunningham et al., 2012; Hallson et al., 2008; Schaaf et al., 2009). Finally, cohesin appears to both positively and negatively affect the transition from paused RNA polymerase to transcription elongation (Fay et al., 2011; Schaaf et al., 2013).

In mammals, cohesin colocalizes with the transcriptional insulator CTCF (CCCTC-binding factor) and mediates transcriptional insulation (Parelho et al., 2008; Wendt et al., 2008). Cohesin performs this function by promoting the formation of chromatin loops in collaboration with CTCF at several loci, including the developmentally regulated interferon γ (Ifng) locus (Hadjur et al., 2009), the apolipoprotein gene cluster (Mishiro et al., 2009), the Igf2/H19 locus (Nativio et al., 2009) and the β-globin locus and the surrounding olfactory receptor genes (Chien et al., 2011; Hou et al., 2010). Cohesin may also affect transcription independently of CTCF, in concert with additional factors. In fact, cohesin colocalizes with the estrogen receptor α at sites not bound by CTCF in breast cancer cells, pointing to a plausible role for cohesin in tissue-specific transcription (Schmidt et al., 2010). In murine embryonic stem cells, cohesin and mediator, a transcriptional co-activator, facilitate DNA looping between the enhancers and promoters of genes required to maintain pluripotency (Kagey et al., 2010). Cohesin also positively regulates the expression of genes such as *Myc* and the protocadherins (Monahan et al., 2012; Rhodes et al., 2010). Of the two versions of cohesin present in somatic cells, cohesin-SA1 and cohesin-SA2, the former appears to play a more important role in the regulation of gene expression. In line with this, mouse embryonic fibroblasts lacking SA1 show a dramatic change in the distribution of cohesin, which shows reduced presence at promoters and CTCF sites. As a consequence, gene expression is altered in a way that affects embryonic development in SA1-null mice (Remeseiro et al., 2012b).

Cohesin and human disease

Cohesinopathies

There are at least two human syndromes related to dysfunction of cohesin: Cornelia de Lange syndrome (CdLS) and Roberts syndrome (RBS). CdLS affects 1:30,000 children and is characterized by both physical and mental developmental anomalies. RBS is a rare disorder characterized by prenatal growth retardation, limb malformations and craniofacial abnormalities. These two cohesinopathies appear to originate from perturbations of different functions of cohesin (Horsfield et al., 2012). More than half of individuals with CdLS present heterozygous mutations in the gene encoding the cohesin loader Nipbl (Nipped-B homolog), whereas mutations in the genes encoding Smc1, Smc3 and Rad21, and the CoDAC Hdac8 (histone deacetylase 8) have been found at lower frequencies (Deardorff et al., 2012). Cells from individuals with CdLS do not display cohesion defects, although they do display increased sensitive to DNA damage (Dorsett and Ström, 2012) and show changes in gene expression (Liu et al., 2009). Mice partially deficient for *Nipbl* recapitulate several features of CdLS, and microarray analyses reveal transcriptional alterations in many genes (Kawauchi et al., 2009). Furthermore, cells from mouse embryos lacking the cohesin subunit SA1 (Stag1), which show a clear developmental delay and die before birth, display both telomere cohesion defects and altered transcriptional profiles related to CdLS that correlate with the presence of cohesin nearby the affected genes (Remeseiro et al., 2012b). Interestingly, *Stag1* heterozygous animals show no CdLS phenotypes, although they have shorter lifespan and increased tumorigenesis. Mice lacking the cohesin regulatory factors Pds5A or Pds5B also die perinatally and show developmental defects that resemble CdLS pathology (Zhang et al., 2009; Zhang et al., 2007); however, gene expression analyses have not yet been reported for these animals.

Drosophila and zebrafish mutants with a reduced dose of Nipbl or cohesin also display altered gene expression and developmental defects, but no chromosome segregation defects (Muto et al., 2011). It is thus likely that gene expression, particularly during development, is much more sensitive to cohesin amount/activity than are other cohesion-related functions, i.e. DNA repair and chromosome segregation. This idea is also consistent with the identification of homozygous mutations in the gene encoding the CoAT Esco2 (establishment of cohesion homolog 2) as the cause of RBS (Vega et al., 2005). Esco2 is essential for cohesion establishment in pericentric heterochromatin (Whelan et al., 2012), which explains the loss of pericentromeric cohesion in chromosomes from individuals with RBS. Intriguingly, Esco2 deficiency in mice results in very early embryonic lethality (Whelan et al., 2012), maybe because the acrocentric nature of mouse chromosomes make them more prone to mis-segregation in the absence of pericentric cohesion. Decreased cell proliferation and increased apoptosis during development are also observed in a zebrafish model of RBS in which Esco2 is depleted (Mönnich et al., 2011).

Very recently, a third cohesinopathy – the Warsaw Breakage syndrome – has been described that shares clinical and cellular features with both RBS and the blood disorder Fanconi anemia. It is caused by biallelic mutation of the gene encoding Chlr1 (also known as Ddx11), a DNA helicase required for proper sister chromatid cohesion in yeast and mammalian cells (van der Lelij et al., 2010).

Cohesin and cancer

In addition to causing cohesinopathies, mutations in cohesin and its interacting factors have been recently linked to cancer. Mutations in the gene encoding the cohesin subunit SA2 (Stag2), which is located on the X chromosome, have been found in a significant number of human tumors (Solomon et al., 2011). As cohesin complexes containing SA2 are responsible for centromeric cohesion, chromosome mis-segregation and aneuploidy in SA2-deficient cells could trigger or promote tumorigenesis. Mice heterozygous for *Stag1* also show increased aneuploidy and tumorigenesis, but through a completely different mechanism that involves impaired telomere replication (Remeseiro et al., 2012a). Intriguingly, mutations in the genes encoding Smc1, Smc3, Rad21 and SA2 have also been found in acute myeloid leukemia, a cancer type that is usually not characterized by aneuploidy (Welch et al., 2012). Whether transcriptional alterations caused by cohesin malfunction contribute to tumorigenesis remains to be addressed.

Perspectives

Cohesin has been classically studied for its role in chromosome segregation and DNA repair. However, intriguing reports from *Drosophila* genetics, published more than a decade ago, hinted to a role for cohesin in promoting the activation of developmental genes by distal enhancers. The importance of cohesin in regulating gene expression is today beyond doubt, but we are still far from understanding the molecular mechanisms responsible for this regulation. The additional roles of cohesin in cohesion, replication and recombination also contribute to position this complex at the center stage of embryonic development. Continued work in different model systems and the use of diverse experimental approaches will allow us to better understand how the cohesin complex works and how it is regulated. Moreover, this knowledge may provide important hints to improve the diagnosis and treatment of human diseases originating from mutations in cohesin and its regulators.

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Competing interests statement

The authors declare no competing financial interests.

Development at a Glance

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