

Sister chromatid cohesion: the beginning of a long and beautiful relationship

Douglas E Koshland* and Vincent Guacci†

Our understanding of the mechanism of sister chromatid cohesion has advanced significantly with the recent identification and characterization of important regulatory factors, structural factors and chromosomal cohesion sites. These analyses reveal a surprisingly complex mechanism of cohesion that is just beginning to be elucidated and exciting connections between cohesion, cell-cycle regulation and other forms of DNA metabolism.

Addresses

*Howard Hughes Medical Institute, Carnegie Institution of Washington, Department of Embryology, 115 West University Parkway, Baltimore, MD 21210, USA; e-mail: koshland@ciweb.edu

†Fox Chase Cancer Center, 7701 Burholme Avenue, Room W462, Philadelphia, PA 19111, USA

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Abbreviation

SMC structural maintenance of chromosomes

Introduction

During mitosis replicated chromosomes (sister chromatids) are segregated into newly-forming daughter cells to ensure that they inherit a genome identical to the parental cell. This segregation represents an unusual sorting process because the two sister chromatids are identical macromolecules that must be moved to different places. Usually, active sorting mechanisms transport identical molecules to the same place, for example the specific compartmentalization of proteins by the secretory apparatus. Alternatively, a passive mechanism like diffusion can distribute identical molecules to different places, but the fidelity of this mechanism is limited by its stochastic nature.

To solve the unusual constraints of sister chromatid sorting, eukaryotic cells have evolved three structures: first, the spindle, a complex microtubule machine; second, the centromere, a specialized locus of the chromatid that organizes the assembly of a microtubule-binding complex called the kinetochore; and third, sister chromatid cohesion, cross-links between sister chromatids that form during DNA replication and persist until the onset of segregation in anaphase. These cross-links exist along the entire length of the sisters. Cohesion proximal to the centromeres is thought to orientate sister kinetochores so that they tend to attach to the microtubules emanating from opposite spindle poles. After kinetochore–microtubule attachment, each sister chromatid experiences microtubule-dependent poleward forces. These opposing forces are not powerful enough to overcome cohesion and initiate

segregation of the sister chromatids, but instead they generate tension on them. Tension on all pairs of sister chromatids is thought to be a signal for their successful bipolar attachment and for the cell to inactivate cohesion and initiate anaphase [1].

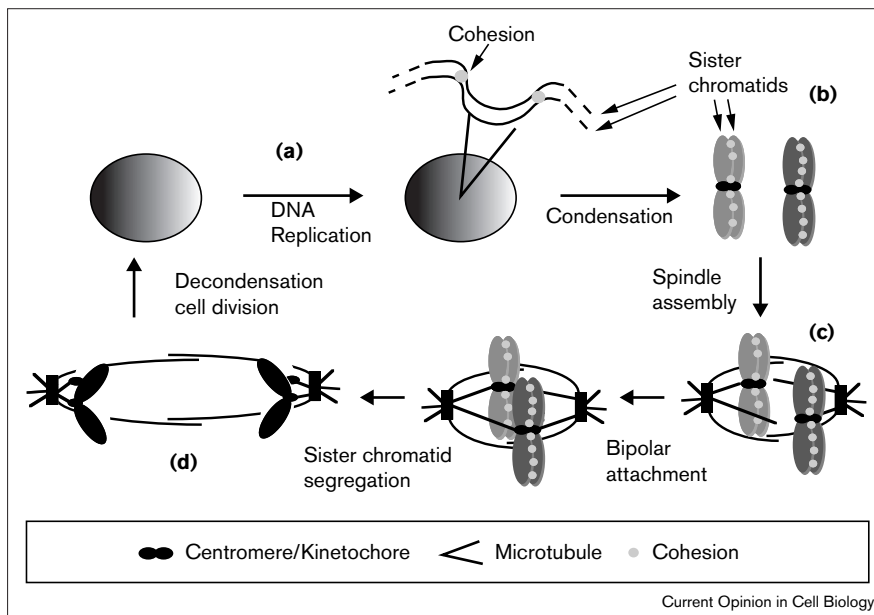
Given the fundamental role of cohesion in ensuring the proper segregation of sister chromatids, it is paramount to understand the molecular basis of cohesion and its regulation. The analysis of cohesion can be divided into three questions: what is the nature of the *trans* and *cis* factors that mediate cohesion, how is cohesion established and how is it dissolved. These questions have been partly answered by exciting new observations of cohesion in both mitosis and meiosis. Their impact has been summarized in an excellent review [2]. However, these observations also reveal that the mechanism of cohesion and its biological significance are only beginning to be elucidated. In this review, we emphasize additional unresolved issues, with a particular focus on mitotic cohesion.

Candidates for the ‘glue’

There are two obvious criteria for the ‘glue’ molecules that directly hold sister chromatids together. First, they must be necessary for the maintenance of sister chromatid cohesion — that is their inactivation after cohesion is established should cause sister chromatid dissociation. Second, these ‘glue’ factors should be present on sister chromatids at least from S to M phase, as this is the window of the cell cycle when cohesion is maintained [3,4]. In budding yeast these criteria have been met by the protein Mcd1/Sccl [5,6]. Additional studies showed that Mcd1/Sccl is in a complex with three other cohesion factors, Sccl, Smc1 and Smc3, and this cohesin complex is conserved from yeast to vertebrates [5,7,8]. Smc1 and Smc3 are members of the SMC (structural maintenance of chromosomes) family of proteins, which have been implicated in recombination, dosage compensation, transcription silencing and chromosome condensation [9,10].

Binding sites for the cohesins Mcd1/Sccl and Smc1 have been identified in budding yeast along chromosome arms and proximal to the centromere [11–13]. The centromere-proximal binding of these cohesins is mediated by two short centromere DNA elements (together with associated factors) that also specify assembly of the kinetochore, thus providing a means to coordinate kinetochore and cohesion activities [13,14]. Remarkably, this centromere site promotes the binding of multiple cohesin complexes contiguously along several Kb of chromatin flanking the centromere, perhaps through cooperative interaction of cohesin subunits [12]. Moreover, the centromere is needed to maintain this extended cohesin-binding domain [12].

Figure 1



Sister chromatid cohesion. **(a)** Chromosomes undergo DNA replication to form two sister chromatids. Cohesion occurs concomitantly with replication near the centromere and along the length of the chromatid arms. **(b)** Sister chromatids condense and the spindle forms. **(c)** Cohesion between sister chromatids sterically constrains the orientation of the centromere/kinetochore so that they favor attachment to microtubules from opposite poles. **(d)** At the onset of anaphase, cohesion is dissolved and sister chromatid segregation ensues. Note that while cohesion is dissolved, at least some of the factors (not shown) that mediate cohesion may remain on the chromatids for a significant portion of anaphase.

The identification of arm sites for cohesin binding has revealed that they occur at ~10 Kb intervals [11*,13*]. In addition, for one arm site the DNA sequence capable of recruiting cohesins has been defined to a 200 bp region [13*]. Whether arm sites act like the centromere site to promote contiguous binding of cohesin complexes onto flanking chromatin has not yet been tested. Also, although both arm and centromere proximal sites appear to have a preference for AT rich DNA [11*,12*], the arm sites do not bind the centromere factors necessary for cohesin loading on to centromere-proximal DNA [12*,13*,15]. Therefore, the mechanism of cohesin loading at arm and centromere sites must differ at least one step.

It is tempting to assume that these cohesin-binding sites must mediate cohesion. However, cohesin subunits also function in recombination and gene expression [16–18]. Therefore, testing a cohesin-binding site for cohesion function is necessary. Devising such a test is difficult in the context of a normal chromosome because both cohesion and the cohesin-binding sites are extensively redundant along the length of the sister chromatids. This problem can be circumvented in budding yeast by exploiting very small (5–15 Kb) minichromosomes with inherently fewer numbers of these sites [14*]. Using these minichromosome-based assays, the cohesin-binding sites proximal to the centromere and at one arm site they have been shown to mediate cohesion [13*,14*]. However, 16 copies of the arm site were required to see significant cohesion activity, suggesting the possibility that this cohesin-binding site may have only weak cohesion activity in its endogenous location [13*]. The possibility of cohesion sites with different strengths is intriguing, given the potential roles of cohesion in chromosome structure and function (see below).

The identification of cohesins and cohesin-binding sites naturally leads to a simple model where a cohesin complex with two DNA-binding domains tethers sisters together by binding the homologous cohesin sites on sister chromatids. However, it seems unlikely that the mechanism of cohesion is so simple. First, the SMC family of proteins has been implicated in several aspects of DNA metabolism, other than binding to double-stranded DNA. In fact, the mammalian cohesin subunits Smc1 and Smc3 also participate in another complex that functions in recombination and repair [17]. SMC family members that are components of the condensin complex modulate DNA topology *in vitro* and possibly *in vivo* [19–22,23*]. Bacterial SMC family members have ATP-dependent, single stranded DNA-binding and aggregating activity [24]. Taken together, these results are consistent with the idea that the common function of SMC molecules, including those in cohesin complexes, is to mediate the formation of specific topological states. One idea is that cohesins generate a chromatin topology that is recognized by a specific chromatid cross-linker. Whether this cross-linker is one of the known members of the cohesin complex is unclear, and in fact, one additional cohesion factor, Spo27/Pds5, has already been identified [25*]; V Guacci and DE Koshland, unpublished data).

A simple cohesion mechanism is also unlikely given the large cohesin-binding domains and the dynamic association of cohesin subunits with chromatids. It will be interesting to determine whether these large domains act as a molecular ‘velcro’ in which cooperative interactions between neighboring cohesin complexes strengthen cohesion. In eukaryotic cells other than budding yeast, the majority of cohesins bound in interphase leave the chromatids prior to metaphase [8*,26,27]. This extensive

remodeling may indicate a reduction in cohesion to accommodate DNA condensation or the replacement of the cohesins by other cohesion factors. Additional remodeling of cohesion may occur, as evidenced by mitotic studies of Mei S322 (the meiotic cohesion protein of *Drosophila*). Intriguingly, in somatic cells Mei S322 does not associate with centromere-proximal regions until prometaphase [28*,29]. Finally, in budding yeast cohesin subunits leave the chromatid at different times during anaphase [7*]. Thus, although the identification of cohesins and their binding sites represents a major advance, the complex activities of SMC-related complexes, the broad cohesin-binding domain, and the dynamic nature of both the cohesin complex and its chromatin binding, suggest that the mechanism of sister chromatid cohesion is just beginning to be elucidated.

Establishing cohesion

A dilemma is posed by the fact that the same cohesion factors mediate cohesion of all sister chromatids [5,6]. What provides the specificity that ensures that cohesion factors 'glue' only sister, but not non-sister chromatids, together? This specificity cannot be dictated solely by homology because cohesion does not occur between homologous chromosomes. The major, if not the only, distinction between sister chromatids and homologs is that sister chromatids are the product of the same replication event. These constraints lead to a model in which cohesion is established during DNA replication [7*,30*]. The proximity of newly-synthesized DNA behind the replication fork drives cohesion factors to bind homologous cohesion sites on sister chromatids rather than homologous sites on homologs, nonhomologous sites on other chromosomes or even nonhomologous sites on the same sister chromatid.

The coupling of cohesion and DNA replication is supported by several observations. The temporal analysis of cohesion in mammals and yeast revealed that cohesion along much of the sister chromatids is established during S phase and maintained until anaphase [3,4]. Transient inactivation of the yeast protein Mcd1/Sccl during M phase results in loss of cohesion and cell death, indicating that cohesion cannot be re-established during M phase [5]. Furthermore, retarding the expression of Mcd1/Sccl until after DNA replication results in cohesin binding to chromosomes but a failure to establish functional cohesion [31*].

The establishment of cohesion appears to require factors that couple it to replication, as well as cohesin loading factors. The Ctf7/Eco1 protein has been shown to function during S phase to establish cohesion, but not during M phase to maintain cohesion [7*,30*]. In addition, this protein exhibits genetic interactions with PCNA, an established elongation factor [30*]. This leads to an attractive model in which PCNA, perhaps along with Ctf7/Eco1, acts behind the replication fork to establish cohesion. However, to date, no direct physical interactions between

cohesins, Ctf7/Eco1 or PCNA have been shown. In the absence of Ctf7/Eco1 or DNA replication, cohesins can still associate with chromatids, but they fail to establish cohesion [7*,31*]. This suggests that Ctf7/Eco1 facilitates the formation of cohesion by coupling cohesin loading with DNA replication, but Ctf7/Eco1 is not required for the loading *per se*. A potential candidate for a loading factor is Sccl/Mis4 [6,7*,32]. In budding yeast this protein is required for the stable association of cohesins with chromatids, but is not part of the cohesin complex. Further analysis of Ctf7/Eco1 and Sccl/Mis4 is likely to provide pivotal insights into the mechanism of cohesion establishment.

The dissolution of cohesion

The timing of cohesion dissolution at the onset of anaphase must be tightly controlled because the precocious inactivation of cohesion can be disastrous, particularly if not all pairs of sister chromatids have made a bipolar attachment. A breakthrough in elucidating this timing mechanism came with the identification of an anaphase inhibitor in budding yeast (Pds1), fission yeast (Cut2) and vertebrates (vsecurin) [33–36]. The activity of these inhibitors is controlled by their ubiquitin-dependent proteolysis, which is mediated by the cyclosome/anaphase promoting complex. Although these proteins share no significant similarity, they bind to a related group of proteins that includes Cut1 and Esp1, conserved from yeast to vertebrates [35,37,38]. Recent evidence in budding yeast shows that Mcd1/Sccl is degraded in an Esp1-dependent manner. An allele of Mcd1/Sccl (ScclRR-DD) has been isolated that blocks its cleavage, its dissociation from sister chromatids and the dissolution of sister chromatid cohesion. This has led to a model in which the proteolysis of Pds1 by cyclosome/anaphase promoting complex releases Esp1, which in turn leads to the cleavage of the Mcd1/Sccl cohesin subunit and to the inactivation of cohesion [39*].

Although this model represents an attractive synthesis of existing results, many questions remain unanswered. Is cleavage of Mcd1/Sccl the cause of sister chromatid dissolution or the consequence? The primary defect of the ScclRR-DD mutant could be its failure to dissociate from chromatids, which in turn blocks its subsequent degradation. Is Esp1 the protease that cleaves Sccl/Mcd1, given that it lacks sequence similarity to known proteases, or is it an activator of a protease [39*]? Is this mechanism of inactivation conserved — as the cleavage site defined in Sccl apparently is not conserved in the Sccl homologs of other organisms? Furthermore, because budding yeast cells can survive inactivation of Pds1 (albeit poorly), there is likely to be another, Pds1-independent, pathway for controlling the dissolution of cohesion [33]. In fission yeast the Cut1/Cut2 complex can be detected on spindles rather than chromosomes, and mutations in Esp1, Cut1, Cut2 and Pds1 cause spindle and cohesion defects [37,40–42]. These observations suggest that Esp1, Cut1 and their associated inhibitors may have additional regulatory activities in spindle morphogenesis and function. This battery of

unanswered questions makes it clear that our current understanding of sister chromatid dissolution is just the tip of the iceberg, and further analyses are likely to provide important insights into cell-cycle regulation.

Conclusion: other functions of cohesion in chromosome structure and genomic stability?

In principle, the bipolar attachment of sister chromatids requires only cohesion proximal to the centromere. If this is the case, what is the function of cohesion along the arms? One possibility is that arm cohesion reinforces centromere cohesion. Although there is evidence to support this [12*,13*], it seems likely that arm cohesion has additional functions. Indeed, inactivation of cohesion factors Mcd1/Scc1 and Pds5 in budding yeast and Spo76 in *Sordaria* causes condensation, as well as cohesion defects ([5,25*]; V Guacci, DE Koshland, unpublished data). It is thought that condensation proceeds in part by the formation of symmetrical loops on sister chromatids. It has been postulated that these loops can be formed by the coalescence of adjacent cohesion sites along the length of paired sister chromatids [5]. The larger the spacing between cohesion sites, the greater the loop size and the greater the compaction. Consistent with this model the condensation of budding yeast chromosomes during mitosis leads to just a two fold compaction, relative to their interphase length. This low level of compaction predicts small loop sizes and high density of cohesion sites. Indeed, cohesin-binding sites occur on average at 10 Kb intervals along chromosome arms [11*,13*]. It will be exciting to determine the position of cohesion sites in organisms like mammals that compact their chromosomes five fold more than budding yeast [5]. It should be noted that in *Xenopus*, the connection between cohesion and condensation is less clear, as immunodepletion of cohesins *in vitro* does not prevent condensation, and no interaction can be detected between soluble cohesins and condensation factors [8*]. However, the *Xenopus* results suffer from two caveats: significant cohesion remained after immunodepletion, and many proteins interact only when bound to chromatin [16].

Arm cohesion may also play important roles in genome stability. When a DNA lesion on one sister chromatid is repaired by recombination, the other sister is the preferred template (rather than the homologous chromosome) presumably because of its proximity [43]. Thus, arm cohesion may serve to limit mitotic homolog exchange and the potentially deleterious effects of homozygosity of recessive alleles. When a DNA lesion occurs in a repetitive DNA sequence, it can stimulate unequal sister chromatid exchange. Recently, analysis of the cohesin sites in the tandem array of rDNA repeats of budding yeast suggests that all repeats have a single cohesin-binding site and most are occupied (S Laloraya, DE Koshland, unpublished data). If these cohesin sites function in cohesion, then the cohesion associated with each repeat may keep the repeats in register to minimize unequal sister chromatid exchange and to maintain rDNA

copy homeostasis. In summary, the identification of cohesion factors, cohesion-binding sites and cohesion regulators provides the tools to elucidate the surprisingly complex mechanism of cohesion and to test its potential integration with other forms of DNA metabolism.

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