

# An update on cohesin function as a 'molecular glue' on chromosomes and spindles

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One of the critical events in mitosis is proper sister chromatid cohesion, which is mediated by a protein complex called cohesin. The cohesin complex is best known for its role in tethering the sister DNA molecules. This review summarizes recent progress in understanding the functions of cohesin, and of its major subunits, SMC1, SMC3, Scc1 and Scc3. It is now clear that cohesin also plays crucial roles in controlling transcription and gene expression, DNA damage repair and spindle pole formation; functions that are beyond the traditional view of cohesin as a 'molecular glue' that holds sister chromosomes together.

## Introduction

During every cell cycle, segregation of chromosomes must take place to ensure that each daughter cell receives exactly one copy of the genome to maintain the genetic stability of the species. One of the most important mechanisms of this process is the splitting of sister chromatids during the metaphase-anaphase transition so that two daughter cells will be given the same chromosome number as the original mother cell. Failure to perform this process precisely results in aneuploidy. To avoid aneuploidy, mitotic cells have developed several safeguard mechanisms to ensure faithful chromosome separation; intimately involved in these mechanisms is a multi-protein complex known as cohesin, which acts as a 'molecular glue' and plays key temporal and spatial roles in the regulation of the metaphase-anaphase transition.

Cohesin was first described in the mid-1990s<sup>1-3</sup> and was shown to prevent premature separation of sister chromatids. Its dissociation from chromosomes during anaphase activates sister chromatid separation, which is directly regulated within the cell cycle. During mitosis, the Anaphase Promoting Complex/Cyclosome (APC/C)<sup>4</sup> and mitotic cyclins regulate cohesin discharge from chromosomes.<sup>5</sup> It has long been supposed, but never proven, that kinetochores form rather rigid polar structures, that sister chromatid cohesion guarantees that sister kinetochores are held back to back with their microtubule-attaching surfaces facing in opposite directions, and that attachment of one surface to stiff

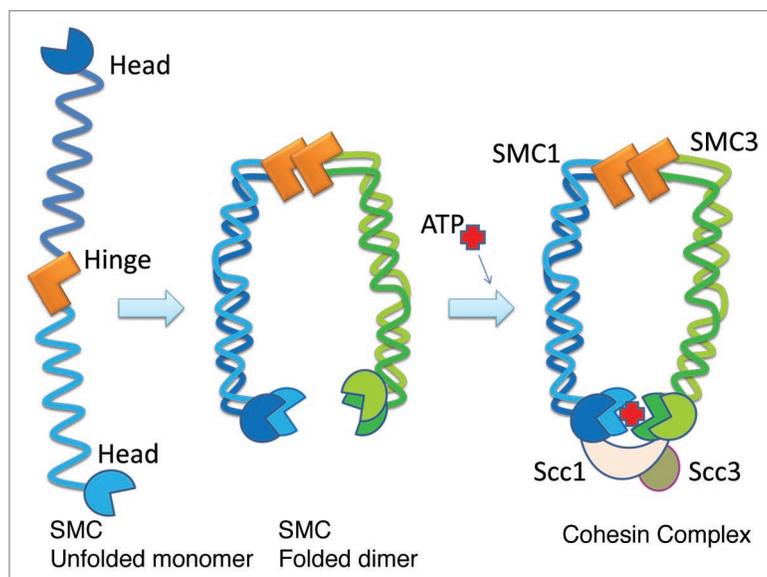
microtubules from one pole would per se preclude attachment of the sister to the same pole.<sup>6</sup> Once bi-orientation has been accomplished, destruction of sister chromatid cohesion must occur to initiate the separation of sister chromatids at the metaphase-to-anaphase transition.<sup>6,7</sup> The proper alignment and attachment of chromosomes to microtubules silences the spindle assembly checkpoint (SAC), which otherwise suppresses APC/C activity. Elevated APC/C activity, upon SAC silencing, permits the targeting of securin and cyclin-B for degradation, thus releasing the separate protease which cleaves cohesin, resulting in sister chromatid separation and mitotic exit.<sup>5,6,8,9</sup>

Apart from its role in holding chromosomes together in mitosis, new roles for cohesin in DNA damage repair, gene regulation and spindle pole formation have been described in the past few years.<sup>6</sup> Here, I briefly summarize what is currently known about cohesin and the topology of cohesion and I also discuss cohesin's potential function as a 'molecular glue' on chromosomes and spindles.

## The Architecture of Cohesin and the Topology of Cohesion

The cohesin complex is conserved from yeast to man and is best known for its role in sister chromatid cohesion. A core cohesin complex contains two SMC (Structural Maintenance of Chromosomes) proteins, SMC1 and SMC3, and two non-SMC proteins, Scc1 (also known as Mcd1 and Rad21) and Scc3 (known in mammalian cells as the SA1 and SA2 isoforms). All components of the cohesin complex are essential for maintaining sister chromatid cohesion in post replicative yeast cells (Fig. 1).<sup>1,6,10-12</sup> These SMC complexes also mediate higher-order changes in chromosome structure, presumably by tethering chromatin.<sup>13,14</sup> SMC proteins are exceedingly conserved not only in sequence but also in structure. The coiled coil regions of Smc1 and Smc3 in mammalian species have an amino acid sequence variation of only around 0.1%.<sup>15,16</sup> Similarly, the coiled coils in the SMC1/SMC3 insect homologues, including *Drosophila melanogaster* and mosquitoes show well-built structural conservation,<sup>16</sup> indicating the conserved relationship across species between cohesin structure and function. In all species studied, after the chromosomes have become bi-orientated on the spindle, sister chromatid disjunction is triggered by site-specific cleavage of the Scc1 subunit of cohesin by separase.<sup>14</sup>

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**Figure 1.** The schematic architecture of SMC proteins and cohesin. The folded SMC monomer includes hinge and head domains connected by a long coiled coil. (Middle) SMC dimers form by association of the hinges and ATP-dependent interaction of the heads (Right). Scc1 then combines the head domain with ATP and later engages Scc3 to form cohesin complex. Figure modified from Onn et al. 2008 and Nasmyth et al. 2009.

The heart of the cohesin complex is the heterodimer formed between SMC1 and SMC3 subunits.<sup>6,13</sup> Each subunit, composed of a 50 nm-long intramolecular anti-parallel coiled coil, forms a rod-shaped protein with a globular “hinge” domain at one end and an ATP nucleotide-binding domain (NBD) of the ABC (ATP binding cassette) family at the other.<sup>6,13</sup> A V-shaped heterodimer forms as soon as SMC1 and SMC3 proteins dimerize through their hinge domains (Fig. 1). The two globular heads of the V-shaped dimer are then joined by the cleavable Scc1/Rad21/Mcd1 subunit, forming coiled coil regions that divide the hinge domain from globular head domain. The crystal structure of the SMC1 ATPase together with the C-terminal domain of Scc1 reveals that Scc1 forms a winged helix capable of binding a pair of  $\beta$  strands in the ATPase head of SMC1, thus promoting the binding of ATP to SMC1.<sup>13,14,17</sup> Scc1 also links Scc3/SA to the complex to form the complete cohesin complex.<sup>11</sup> The data from recent FRET experiments indicate, however, that the Scc1 C-terminus lies between the SMC heads, which would always be in contact with each other.<sup>12,18</sup> Moreover, recent studies have indicated the importance of the hinge domain in this process and even proposed that opening of the ring may occur at the hinge instead of the head domains.<sup>12,19-21</sup>

Several cofactors assist in sister chromatid cohesion enforced by the cohesin complex. These are the HEAT repeat protein Pds1, Scc2/Nipbl, TPR protein Scc4, acetyl transferase Eco1 and Sororin.<sup>6</sup> Interestingly, at least three groups independently<sup>22-24</sup> demonstrated in yeast and mammals that Smc3 is acetylated by Eco1,<sup>25</sup> a conserved acetyltransferase, during DNA replication to promote sister chromatid cohesion. These results strongly suggest that Eco1 modifies cohesin to stabilize sister chromatid cohesion

in parallel with a cohesion establishment reaction and that SMC3 acetylation provides important insights into the mechanism of cohesion establishment.<sup>22-24</sup>

### Cohesin Function as a ‘Molecular Glue’ that Tethers Sister Chromosomes: Ring or Handcuff?

Even though the structure of cohesin has been well characterized, an argument still exists concerning the mechanism of its binding to DNA and subsequent establishment of cohesion between two sister chromatids.<sup>13,20</sup> There are two major models of cohesin binding to capture DNA and to form a cohesion complex: Ring or Handcuff.

Cohesin rings<sup>26</sup> have a diameter between 30–35 nm, which is considerably larger than an extended 10 nm nucleosomal chromatin fiber. Therefore, sister DNAs could be trapped inside a covalently circularized cohesin ring.<sup>6</sup> In this ring model the soluble chromatin-free ring is the relevant structure for both chromatin binding and tethering. As originally postulated, this ring model proposes that ATP hydrolysis by the cohesin heads causes them to dissociate and the ring to open. Opening of the ring allows nucleosomal DNAs of the two sister chromatids to enter the interior of the ring, either simultaneously or sequentially. The sister chromatids are then entrapped when the ring reforms by the re-association of the head domains through the binding of ATP. The Scc1 kleisin subunit closes the other end of the ring.<sup>6,13</sup>

The Handcuff model suggests that cohesion is established by protein-protein interactions between cohesin complexes that are individually bound to each sister chromatid.<sup>13,27-29</sup> The Handcuff model<sup>28,29</sup> suggests that the tethering of two separate cohesin rings occurs through interactions between Scc3 (SA1 or SA2) molecules, or by the two Scc1/Rad21 molecules of the cohesin complexes.<sup>28-30</sup> Three of the four core cohesin subunits (Rad21, SMC1 and SMC3) interact with themselves and with each other, whereas the two Scc3 orthologs, SA1 and SA2, cannot. Evidence in support of the handcuff model include these molecular associations between cohesin subunits, as well as the results of a fluorescence protein complement assay (PCA), protein-protein interactions from a yeast two-hybrid assay and studies of SA1 and SA2 depletion using siRNA.<sup>28,29</sup> The handcuff model predicts two rings, each of which has one set of Rad21, Smc1 and Smc3 molecules. The handcuff is established when two Rad21 molecules move into antiparallel orientation that is enforced by either SA1 or SA2.<sup>28</sup> This handcuff model requires that only one DNA strand of chromatin is ensnared in a single cohesin complex.<sup>31</sup> The ring model suggests that cohesin does not bind to DNA, but rather the cohesin complex encloses DNA. This is consistent with evidence that cohesion is disrupted when circular minichromosomes are cut or when the cohesin complex is opened.<sup>32</sup> A major criticism of the ring model is that it cannot explain the observation that cohesin is localized at specific sequences along the genome.<sup>6,30</sup> Studies in support of the handcuff model rather

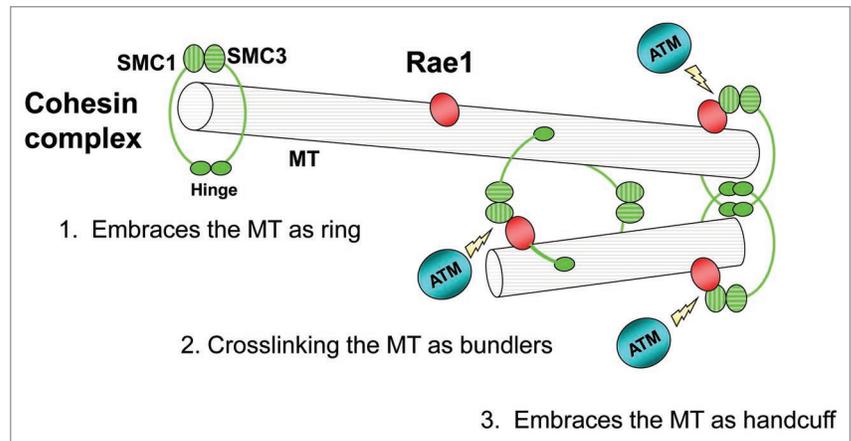
suggest that the cohesin complex does bind to DNA. A concern with the handcuff model is that some experiments supporting it involved protein overexpression, which is known to facilitate interactions between separate SMC1/3 heterodimers.<sup>6</sup>

Even though evidence supports both the ring and handcuff models, many aspects of how cohesin binds and entraps DNA are still blurred. The one-ring embrace model currently predominates in the field; however, future research will resolve discrepancies in these models. Indeed, the true mechanism of cohesin binding may be a mixture of both the ring and handcuff models.

There are already several excellent reviews<sup>6,9,12,33,34</sup> detailing the loading of cohesin onto chromatin, the establishment of cohesion; cohesin removal from the chromosomes during prophase and anaphase and cohesin cleavage by separase, or cohesin functions in transcriptional regulation, and in DNA damage repair. I do not discuss these issues further; rather I focus on roles of the cohesin complex in spindle formation.

### Cohesin Function as a 'Molecular Glue' on Spindle Poles/Centrosomes?

A developing body of evidence indicates that human cohesin interacts with the Rae1 (RNA export factor 1)/Gle2/mrnp41-NuMA (Nuclear Mitotic Apparatus protein) subcomplex, which is localized at the spindle poles<sup>35-37</sup> during mitosis. As a beta propeller protein, Rae1 is ideally suited to serve as a protein interaction platform.<sup>38</sup> We previously reported that microtubule bound Rae1 recruits NuMA<sup>39</sup> to the mitotic spindle. We located NuMA's binding site for Rae1 to an N-terminal segment of NuMA and showed that in vivo expression of this fragment, and imbalances created in this assembly pathway, caused formation of multipolar spindles.<sup>38</sup> Immunofluorescence microscopy has shown the cohesin subunit, SMC3, partially co-localized with NuMA at spindle poles in vitro.<sup>40</sup> To investigate whether Rae1 might be involved in the recruitment of cohesin subunit SMC1 to mitotic spindle poles, we carried out a series of biochemical experiments and we demonstrated that Rae1 interacts with SMC1 during mitosis. Imbalances in these assembly (Rae1-SMC1-NuMA) pathways caused formation of multipolar spindles. These data indicate that cohesin's known bundling function for chromatids in mitotic and interphase cells extends to microtubules at the spindle pole.<sup>35,36</sup> It is possible that the spindle pole bound SMC1/SMC3 heterodimer recruits the other members of the cohesin complex, Scc1 and Scc3, thereby completing closure into a circular structure. Hence, cohesin would function to embrace microtubules at the spindle pole, extending its known function in encircling nucleosomal DNA of sister chromatids (Fig. 2). The specific role of the mitotic Rae1-SMC1 complex in vivo is further shown by the overexpression of SMC1, which caused aberrant multi-polar spindles, and by the depletion of SMC1 by RNAi,



**Figure 2.** A speculative model of cohesin function at the spindle pole. Cohesin may (1) embrace the microtubules (MTs) as a ring, in a similar manner to embracing DNA in sister chromatids, or (2) crosslink the MTs together to form MT bundles or (3) embrace MTs according to the handcuff model.

which caused cytokinesis defects.<sup>35</sup> An SMC1 mutant, defective for Rae1 binding, could not rescue the cytokinesis defects generated by SMC1 RNAi. Together with our recent work, I propose a speculative model in which the cohesin complex either embraces or handcuffs microtubules (Fig. 2).<sup>35</sup>

Similar studies by other groups have independently confirmed that not just SMC1 but probably the whole cohesin complex associates with microtubules at the spindle pole<sup>37</sup> and at centrosomes.<sup>41</sup> Localization of Rad21 (DRAD21) at spindle poles was reported previously in *Drosophila*,<sup>42</sup> but whether it is at spindle poles in other species was largely unknown. In this special issue of *Cell Cycle*, three papers from the Clarke group further confirmed that the mammalian cohesin subunit, Scc1/Rad21, indeed localized at the spindle poles/centrosomes through very detailed live imaging and RNAi depletion assays.<sup>43-45</sup> Beauchene et al. found that Rad21 is required for centrosome integrity in human cells independently of its role in chromosome cohesion.<sup>43</sup> Giménez-Abián et al. showed that the cohesin protein Rad21 localizes to centrosomes in a manner that is dependent upon known regulators of sister chromatid cohesion as well as regulators of centrosome function.<sup>45</sup> Consistently, Díaz-Martínez et al. presented data indicating that after Rad21 depletion, chromosomes align at the metaphase plate and bipolar spindles assemble in most cases, but in anaphase the separated chromatids segregate to multiple poles. They performed time-lapse microscopy revealing that the spindle poles often become split in Rad21-depleted metaphase cells. Interestingly, exogenous expression of non-cleavable Rad21 resulted in multi-polar anaphases. These new data are consistent with a non-chromosomal function of cohesin.<sup>44</sup>

In addition, Nakamura et al. discovered that centrosomes harbor the protein Aki1 (Akt kinase-interacting protein 1), which promotes centriole integrity. Interestingly, Aki1 interaction with cohesin subunit Scc1 prevents centrioles from splitting too soon; Aki1 also binds another cohesin component, SA-2. These results further confirm that the cohesin complex localizes around the spindle pole/centrosome region.<sup>46</sup>

Indirectly supporting these findings, recent studies have also characterized roles for Sgol and separase, beyond their roles in sister chromatid cohesion, in centriole replication and duplication. For instance a short spliced variant of Sgol (sSgo1) functions specifically in centriole cohesion<sup>47</sup> and polo kinase and separase regulate mitotic cleavage of cohesin as well as centriole duplication in human cells.<sup>48</sup> These data suggest that the cellular machinery used in sister chromatid cohesion and separation may function in a similar manner at spindle poles/centrosomes.

However, it is unclear how cohesin actually influences spindle pole/centrosome activity.<sup>6</sup> Kong et al.<sup>37</sup> suggested that loss of cohesin from centrosomes disrupts the association of essential centrosome components, perhaps affecting centrosome integrity and function. Alternatively, but not mutually exclusively, cohesin may directly contribute in microtubule nucleation/assembly. Since purified cohesin (resistant to a 1 M salt wash) has the ability to restore spindle assembly activity in vitro, this strongly suggests that cohesin itself, and not necessarily an associated factor, is functionally important. We suggest that cohesin may (1) embrace microtubules as a ring, in a similar manner to embracing DNA in sister chromatids,<sup>35,36</sup> (2) crosslink the microtubules together to form MT bundlers, (3) embrace microtubules according to the handcuff model (Fig. 2). Future studies will determine the exact function of cohesin in facilitating centrosome and spindle pole activity.

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Given the recent flood of cohesin papers,<sup>21,49-55</sup> in particular the new area of cohesin subunits on spindle poles/centrosomes,<sup>35-37,41,43-46</sup> with nearly every finding in the field being made simultaneously by multiple labs, we may expect to see rapid progress in cohesin research related to spindle pole/centrosome biology. It will be a great future challenge to understand when and how different functional connections arise between components of cohesin during evolution. We can be assured that whether by chance or by design, cohesin subunits will continue to announce themselves and receive their day in the scientific limelight.

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