The torments of the cohesin ring

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ABSTRACT
Cohesin is a ring-shaped protein complex which comprises the Smc1, Smc3 and Scc1 subunits. It topologically embraces chromosomal DNA to connect sister chromatids and stabilize chromatin loops. It is required for proper chromosomal segregation, DNA repair and transcriptional regulation. We have recently reported that cohesin rings can adopt a “collapsed” rod-like conformation which is driven by the interaction between the Smc1 and Smc3 coiled coil arms and is regulated by post-translational modifications. The “collapsed” conformation plays a role in cohesin ring assembly and its loading on the DNA. Here we speculate about the mechanism of cohesin’s conformational transitions in relation to its loading on the DNA and draw parallels with other Smc-like complexes.

KEYWORDS: acetyltransferase; ATPase; chromosomes; cohesin; sister chromatid cohesion

Introduction
In eukaryotic cells, chromosomal DNA is threaded through the proteinaceous cohesin rings. A fraction of cohesin rings embrace 2 sister DNA molecules and function in sister chromatid cohesion. Cohesion between sister chromatids is essential for their proper segregation to daughter cells during cell division and for double-strand break repair by homologous recombination. Other cohesins stabilize loops within the same chromatid to define the boundaries of chromatin domains and regulate transcription. A topological mode of association between cohesin rings and the DNA is thought to provide a very stable connection between 2 DNA molecules or 2 parts of the same DNA molecule while the very large size of the rings, which are estimated to be about 35 nm in diameter, ensures minimal interference with DNA metabolism. However, the molecular mechanism of how the cohesin ring entraps sister chromatids remains to be unraveled.

The cohesin ring is composed of the Smc1, Smc3 and Scc1 subunits and associates with the additional Scc3, Pds5 and Wpl1 proteins. The Smc1 and Smc3 fold into long anti-parallel intramolecular coiled coils, or arms, which form the circumference of the ring. The coiled coils are flanked by the globular hinge and head domains. The head is composed of the N- and C-terminal regions of the Smc protein which fold together into an ABC-type ATPase domain. The Smc1 and Smc3 heads can sandwich and hydrolyze 2 molecules of ATP and are connected by the Scc1 subunit. The Smc1 and Smc3 hinges associate with each other thus completing the ring. While the interaction between the hinge domains is very stable, the heads have a very low affinity for each other even in the presence of non-hydrolyzable ATP. This raises the question of how the rings get assembled in the first place.

The “collapsed” form of cohesin ring
We have recently uncovered evidence that the arms of budding yeast Smc1 and Smc3 associate with each other along their lengths, which brings the heads together in the correct orientation and allows them to be connected by Scc1. Amino acid
substitutions in the coiled coils, which affect association between the Smc arms, disrupt Scc1 recruitment and result in lethality. The Smc coiled coils appear to be highly flexible. The flexibility is probably enhanced by the disordered gaps which intersperse with the coiled coil stretches and can be identified by amino acid sequence analysis. However, when the Smc1 and Smc3 arms are bound together, they form a stable rod-like structure, which we were able to observe by scanning force microscopy (SFM) in solution. The arms in the rod appeared to be tightly intertwined and the overall structure was very compact. Our results are supported by the report from Peters’ laboratory that the cohesin coiled coil arms could be cross-linked using a chemical cross-linker indicating their physical proximity to each other. Very recently, the rod-like form of human cohesin was also observed by electron microscopy. Our ability to follow the individual cohesin complexes over time in solution using SFM further established that the association between the Smc1 and Smc3 arms is not caused by the complexes drying out during the preparation of the sample for electron or scanning force microscopy. The “collapsed” rod-like form of the cohesin ring is likely to facilitate its assembly, intracellular transport and import inside the nucleus and to play a role during cohesin loading on the DNA. Conversely, the Smc arms would need to separate to let the DNA inside the cohesin ring.

**The enigmatic role of ATP hydrolysis**

The cohesin ring is assembled before its loading on the DNA and therefore an interface between either the heads or the hinges needs to open for the DNA to be imported inside it. Evidence that blocking the opening of the interface between the Smc1 and Smc3 hinge domains prevents the loading of cohesin onto DNA was interpreted to indicate that this interface serves as an entry gate. Since loading of cohesin on the DNA in vitro requires ATP hydrolysis by the heads, it was hypothesized that the role of ATP hydrolysis is to facilitate the dissociation of the Smc1 and Smc3 hinge domains. Until now, it was difficult to envision the mechanistic connection between the heads and the hinges since they are separated by a very long coiled coil and do not bind to each other when expressed as individual domains. Our observation of the collapsed form of cohesin ring suggests that the cycle of ATP binding/ATP hydrolysis, which controls engagement/disengagement of the heads, is likely to affect the degree to which the arms are coiled around each other. ATP-dependent head engagement promotes dissolution of the Bacillus subtilis Smc rod and is antagonized by the hinge dimerization. Changes in the degree of ring supercoiling might be the means to transmit the conformational change from the heads to the hinge and force the hinge to open. The cohesin loader protein Scc2, which makes contacts with the Smc arms and with other regions of cohesin, might also be involved in this process (Fig. 1A). Alternatively, the hinge needs to open and close in the process of unraveling the Smc arms and the requirement for ATP hydrolysis stems at least partially from the necessity to separate the arms to let the DNA inside the ring. The recent development of an in vitro DNA loading assay with purified cohesin and cohesin loader should make it possible to address these hypotheses.

Interestingly, small quantities of fission yeast cohesin and human cohesin can both be loaded onto DNA in the absence of ATP and the cohesin loader in vitro. The low level of DNA binding of fission yeast cohesin observed in the absence of the cohesin loader is sensitive to DNA linearization, suggesting that cohesin can load topologically without requirement for the cohesin loader in vitro. However, loading of fission yeast but not human cohesin was greatly stimulated by ATP and the cohesin loader. Attempts to load budding yeast cohesin have been unsuccessful. It is conceivable that cohesin preparations from different species, which are used for the experiments in vitro, differ in relative amounts of different cohesin conformations, e.g., O-shaped vs rod-like. Purified human cohesin is predominantly O-shaped when visualized by rotary-shadowing electron microscopy, although a variety of conformations, including rods, were observed by negative-stain electron microscopy. Budding yeast cohesin is mostly rod-like. While we are not aware of any electron microscopy studies of fission yeast cohesin, it is tempting to speculate that this preparation might be comprised predominantly of the partially collapsed rings. It remains to be investigated whether stability of the rod-like conformation of cohesin varies among species and whether this could contribute to the species-specific differences in the efficiency of cohesin loading in vitro.
Conformational transitions in Rad50/Mre11 vs cohesin

Rod-like forms were reported for cohesin-related bacterial Smc complexes and eukaryotic condensin. Thus, it is likely that all protein complexes containing Smc-like subunits are able to transition between the “arms together” and “arms apart” forms and this transition is important for their function. The long-range allosteric regulation involving coiled coils was studied in the cohesin-related Rad50/Mre11 complex which tethers the ends of broken DNA molecules to facilitate DNA repair. Similar to cohesin’s Smc proteins, Rad50 folds into a long intramolecular coiled coil with globular N- and C-terminal domains. However, instead of a hinge domain, Rad50 contains a central CXXC motif which is called a “zinc hook” and, like the hinge, is also capable of dimerizing. Similar to Scc1, which binds to the Smc3 head-proximal coiled coil via its N-terminal region and to the Smc1 head via its C-terminus, Mre11 interacts with the Rad50 head and the head-proximal region of the coiled coil. However, mutations of the hook disrupted Rad50 interaction with Mre11. Truncation of the hook-proximal Rad50 coiled coil was reported to have a modest effect on sister chromatid recombination but, surprisingly, severely impaired non-homologous end-joining which is thought to be executed by the Rad50 globular domain. It was proposed that changes in the distal regions of the coiled coils might perturb the mutual
orientation of the globular head domains. These results parallel our observation that amino acid substitutions in the Smc coiled coils abolished the recruitment of Scc1, although the sites of Scc1 binding remained unchanged. The most likely explanation is that altered interaction between the Smc1 and Smc3 coiled coils resulted in an incorrect head orientation which precluded them from being connected by Scc1. Conversely, crystal structures of the Rad50 head/Mre11 complex demonstrated that conformational changes accompanying ATP binding by the globular domain reposition the coiled coils, changing the angle at their base. This is consistent with our hypothesis that the cycle of ATP binding/ATP hydrolysis might be coupled to the unraveling of the Smc arms. When human Rad50/Mre11 complex is bound to DNA via its globular domain, the coiled coils are in the “parallel” conformation and move synchronously. This orientation of the coiled coils promotes tethering of the DNA ends by Rad50/Mre11 complexes bound to different DNA molecules. Upon release from the DNA, the Rad50/Mre11 complex assumes an open conformation in which the coiled coils bend independently of each other in either an open or a closed ring-like structure depending on the intra-complex hook dimerization. The conformational cross-talk between the globular and coiled coil domains is likely to be critical for the function of both Rad50/Mre11 and cohesin.

“Collapsed” rings on DNA

An interesting question is whether the collapsed rod-like cohesin rings exist only before loading on the DNA or whether the Smc arms can associate with each other even after the DNA had been captured inside the ring. We were able to crosslink the arms of chromatin-bound cohesins in vivo (Fig. 1B), which suggests that at least some of the chromosomal cohesins have their Smc arms contacting each other and might be in the partially collapsed conformation. This observation is in agreement with the recent reports from Koshland’s and Peters’ groups that fission yeast and human cohesins, which are loaded on the DNA in vitro, can diffuse past DNA-bound proteins smaller than approximately 11 nm but are blocked by the particles of approximately 21 nm. Both groups concluded that the diameters of the cohesin rings, which had been loaded on the DNA in vitro, appear to be smaller than the diameter of an O-form of cohesin ring, which was estimated to be approximately 35 nm. In the in vitro assays, the presumably partially collapsed rings were pushed by the T7 RNA polymerase and the FtsK motor protein. A collapsed ring on the DNA is likely to present an obstacle to transcription, replication, and repair in vivo and might contribute to the reported roles of cohesin in regulating transcriptional elongation and blocking DNA synthesis in the presence of radiation-induced damage.

Role of post-translational modifications

We have demonstrated that the ability of the Smc arms to associate with each other depends on acetylation and possibly other post-translational modifications of the coiled coil lysines. A coiled coil is composed of 2 intertwined α-helices which display a 7 amino acid periodicity in their pattern of hydrophobicity and are held together by a hydrophobic core of amino acids at positions a and d. Side chains of positively charged lysines mostly face the solvent and can be potentially involved in interaction with other proteins, e.g., the coiled coil of the neighboring Smc. Notably, mass-spectrometry identified multiple acetylated and ubiquitylated lysines in the Smc arms. The conservative substitution of lysines for arginines would be expected to have little or no effect on the coiled coil fold but would abolish the post-translational modifications. Remarkably, we were able to show that substitution of an increasing number of lysines for arginines in the Smc1 and Smc3 coiled coils resulted in incremental cohesion defects and eventually in lethality. At the molecular level, mutant cohesins were defective in loading on the DNA and, as more lysines were mutated, lost the ability to recruit Scc1 and connect the Smc heads. Arginine mutants were observed by scanning force microscopy to display altered packing of the Smc arms and treatment of recombinant wild-type Smc1/Smc3 dimers with deacetylase facilitated the arms’ separation. A known example when amino acid charge neutralization by post-translational modifications affects the interaction interface between the long coiled coils is the bacterial chemotactic receptor. In this system, methylation of 4 glutamate residues is thought to increase the packing of the 4-helix bundle generating a conformational adaptation signal which can be transmitted along the coiled coils.
The identity of the acetyltransferases involved in modifying the Smc arms remains to be established. We have discovered that deletions of certain N-terminal acetyltransferases, nat3 (naa20) and ard1 (naa10), result in synthetic sickness when combined with the smc arginine mutants.9 The N-terminal acetyltransferases are known to associate with the ribosomes44 and could potentially modify Smc1 and Smc3 proteins cotranslationally, which would facilitate their heterodimerisation, binding of Scc1 and transport into the nucleus. In addition, human Ard1 was found to translocate into the nucleus.45 However, the reports on the ability of N-terminal acetyltransferases to modify internal lysines46-49 remain controversial,50,51 and our attempts to acetylate Smc proteins in vitro using recombinant Nat3/Mdm20 and Ard1/Nat1 N-terminal acetyltransferases were unsuccessful. It is conceivable that it would be necessary to couple an acetylation assay to an in vitro translation system.

Remarkably, collapsed rings are also found in association with the chromosomes. Since the transition between the collapsed rod-like and the O-forms of cohesin rings is likely to be regulated by post-translational modifications, chromatin-associated lysine acetyltransferases and deacetylases might be able to regulate the extent of Smc arms’ interaction and hence the diameter of the cohesin ring and its ability to slide along the DNA which would in turn affect transcription and repair. Modifying enzymes might also either facilitate or impair cohesin loading at certain genomic loci. This exciting possibility awaits further investigation.

Perspectives

The collapsed rod-like form of the cohesin ring is a functionally important conformation shared by the related protein complexes containing Smc-like proteins. Understanding the role of ATP hydrolysis in the conformational transitions of the cohesin complex will be critical for delineating the molecular mechanism of its loading on the DNA. The combination of the recently established in vitro DNA loading assays and advanced microscopy should provide important insights. The identification of modifying enzymes, which stabilize certain conformations of cohesin is another exciting field of discovery.

Rephrasing the quote from the English playwright Colley Cibber “Oh! How many torments lie in the small circle of a wedding ring!” the “torments” of the cohesin ring bring about unexpected twisted conformations, which are inseparable from its function.

Disclosure of potential conflicts of interest

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