Combing Chromosomal DNA Mediated by the SMC Complex: Structure and Mechanisms

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1. Introduction

The relative simplicity of the structure of bacterial cells has significantly contributed to our understanding of many complex biological systems. Yet in bacteria, the principles of chromosome organization have not fully understood. Bacteria maintain the genetic materials as a compact nucleoid through the action of organization have not fully understood. Bacteria maintain the genetic materials as a compact nucleoid through the action of many nucleoid-associated proteins (NAPs). Among them, the SMC (Structural Maintenance of Chromosomes) protein has been thought to play a static role in the organization and segregation of the chromosome during cell division. However, recent studies have shown that the bacterial SMC is required to align left and right arms of the emerging chromosome and that the protein dynamically travels from origin to Ter region. A rod form of the SMC complex mediates DNA bridging and has been recognized as a machinery responsible for DNA loop extrusion, like eukaryotic condensin or cohesin complexes, which act as chromosome organizers. Attention is now turning to how the prototype of the complex is loaded on the entry site and translocated on chromosomal DNA, explaining its overall conformational changes at atomic levels. Here, we review and highlight recent findings concerning the prokaryotic SMC complex and discuss possible mechanisms from the viewpoint of protein architecture.

Genome maintenance requires various nucleoid-associated factors in prokaryotes. Among them, the SMC (Structural Maintenance of Chromosomes) protein has been thought to play a static role in the organization and segregation of the chromosome during cell division. However, recent studies have shown that the bacterial SMC is required to align left and right arms of the emerging chromosome and that the protein dynamically travels from origin to Ter region. A rod form of the SMC complex mediates DNA bridging and has been recognized as a machinery responsible for DNA loop extrusion, like eukaryotic condensin or cohesin complexes, which act as chromosome organizers. Attention is now turning to how the prototype of the complex is loaded on the entry site and translocated on chromosomal DNA, explaining its overall conformational changes at atomic levels. Here, we review and highlight recent findings concerning the prokaryotic SMC complex and discuss possible mechanisms from the viewpoint of protein architecture.

2. Secrets of the Coiled-Coil Arm in SMC Proteins

What is the role of the long coiled-coil arm of SMC? Recently, the Gruber’s group has tackled this challenging question and succeeded in constructing a structural model of a full-length SMC protein (Figure 2A). First, Bürmann et al. have clarified that the SMC coiled-coil length faithfully reflects a helical periodicity between the two juxtaposed arms. Even among prokaryotic SMC proteins, the primary sequence of the coiled-coil region is not conserved, whereas the length is evolutionarily conserved in several groups, in which contact area between arms appears in multiples of 91 amino acids. The ScpAB subcomplex then forms an asymmetrical bridge between distal tips of the SMC dimer (Figure 1A). Cells lacking any of the genes encoding these three subunits are inviable under fast-growth conditions, however the mutants are viable under slow-growth conditions and produce anucleate cells to some extent. SMC-ScpAB is recruited to a site adjacent to the replication origin in a manner dependent on the Spo0J/ParB partitioning protein bound to bacterial centromeric parS sites. Therefore, the complex is essential for the separation of the newly replicated origin regions. It has been suggested that the SMC ATPase activity drives conversion of the complex into an active ring conformation, which in turn facilitates its targeting to the Spo0J coated DNA region (Figure 1B).
At the distal end, the middle section of the peptide chain forms a coiled-coil interaction. The N- and C-terminal regions fold together into an ATP-binding cassette (ABC)-type ATPase domain for engagement are shown by gray arrows based on crystal structures. Transition state mutations apparently hold in intermediate state by decreasing neighboring charge. These results also provide valuable insights into how a pair of linear structures is aligned dynamically but within a cross-linkable range, over a length of approximately 50 nm.

3. Twisting and Opening Leading to the Asymmetrical Hinge Dimer

To date, a variety of SMC hinge structures from different species have been reported, clarifying the specific folding and conserved basic potential surface. Overall, there are two types of structure observed. One is a symmetrical dimer with rod-like juxtaposed coiled coils, and the other is a dimer with coiled coils protruding in almost opposite directions (Figure 3A). Moreover, a recently solved bacterial hinge exhibits an asymmetrically oriented dimeric structure with a half-opened interface. Structural comparison among twisted hinge structures suggests that the dimer resolves one of the interfaces to expose the conserved basic surface (Figure 3B). This motion is expected when the direction of the coiled-coil domain is changed after head-head engagement; therefore, the hinge domain works as a bimodal switch. The asymmetrical hinge with widely separated coiled coils is structurally relaxed, as the start site of the C-terminal helix of the coiled coil is stably anchored to the domain by its conserved hydrophobic residues (Figure 3A).

The hinge structure with juxtaposed coiled coils is a rather constrained form. Close juxtaposition of the arms creates distortions on their joints of the hinge domain, thereby forcing the anchoring residues to be unplugged and resulting in a symmetrical dimer fold.

4. Potential Dual Regulation by ScpB

Mechanistic details on the ScpAB subcomplex are largely obscure. Different from ScpA, ScpB is not directly involved in formation of the tripartite ring. However, ScpB is essential for triggering the SMC ATPase activity and loading the complex onto chromosomes. One of the key questions is how the SMC is dynamically regulated by these factors. The binding of the ScpA NTD to the SMC neck has been already reported, and probably this feature is common among all the SMC complexes. However, binding of the ScpA NTD to the neck region is also negatively regulated by the ScpBap CTD.
(Figure 3C).

5. The Spo0J/ParB Based Looping of DNA Including parS

In B. subtilis, the chromosomal partition protein Spo0J/ParB forms discrete foci, which colocalise with the origin of replication region. There are ≈1000 Spo0J per the cell, which is a great excess over the eight known parS binding sites. One explanation for this difference is that Spo0J has been shown to associate with several kilobases of DNA that flank its specific binding sites (parS) in vitro. However, such extensive spreading is accomplished by a limited number of dimers in cell (~20 per parS site), suggesting long-range bridging, which is capable of DNA loop formation. A recent study of the C-terminally truncated Helicobacter pylori Spo0J, crystallized with DNA containing the parS sequence, has provided a structural basis for DNA bridging. Each of the Spo0J monomers binds to half of the palindromic parS site through its central DNA binding domain. Then, two of the dimeric Spo0J on DNA oligomerize by their NTDs in both cis and trans (Figure 4A). Mutations of the arginine residues in a highly conserved patch, RRXR of the NTD, lead to severe spreading defects. These data provide a structural basis for the formation of a Spo0J-parS cluster that can bridge and trap large DNA loops.

6. Recruitment of the SMC Complex by the Spo0J-parS Complex

Spo0J is critical for enriching SMC complexes near the replication origin in some bacteria. Previously SMC has been shown to be able to be crosslinked to Spo0J in vivo, indicating protein-protein interactions. Minnen et al. have explained static and dynamic features of the SMC complex, distinguishing the initial targeting and the subsequent relocation to other regions of the chromosome. They found that, as established by subcellular localization studies, targeting of the complex is strictly dependent on SMC head-head engagement (see explanations of each step of the ATP cycle, Figure 1B).
means that proper geometry of the coiled-coil arms by the engagement is a structural prerequisite for this step. Such SMC localization phenotypes are dependent on each step of the ATPase reaction cycle, and a similar classification is also utilized for a study of dynamic behavior of Soj at the stage of DNA replication initiation.[46] Minnen et al. have also found a minimal region including the coiled coil for targeting to chromosomal ParB-parS. The most likely site for interaction with Spo0J is the head-proximal joint region. Conservation of some hydrophobic residues on the surface of this region strongly suggests that this might be the candidate site (Figure 2D). Cells harboring DNA bridging-deficient Spo0J mutants have an abnormal nucleoid morphology and the mutant proteins also show attenuation of chromosome entrapment by the SMC complex.[27,40] However, evidence of stable interactions between these proteins has not been reported yet, therefore, involvements of their hidden interfaces might be considered in the targeting process.

7. Loop Extrusion and Arm Alignment for Bacterial Chromosome Organization

A previous deep sequencing study of the circular Caulobacter crescentus chromosome has clarified that SMC coordinates alignment of the left and right DNA arms which connect the oriC and Ter.[166] Rudner and coworkers have shown that the SMC loading depends on Spo0J and the parS sequence in B. subtilis.[14] Recently, using cells containing only a single parS site, the same group has chased progression of the SMC complex by ChIP-seq and examined the chromosome architecture by time-resolved Hi-C.[47] The authors concluded that the coordinated alignment is directed by continuous loading of SMC complexes at parS rather than sequential loading of new SMC complexes at the leading edge of the juxtaposed DNA and then the complexes move down to the Ter region (Figure 4B). The movement of the complex is replication-independent and its apparent translocation rate is ≈50 kb/min, almost the same order of rate as the replication fork,[48–50] and quite fast compared with a yeast condensin (≈3.6 kb/min).[51] The SMC translocation is slower on either arm, when an ectopic parS site is introduced, and severely inhibited by head-on transcription.[14,37,47] Tran et al. reported that such conflict likely creates an irregular enlargement of the DNA loop that causes SMC stalling or dissociation from either chromosomal arm.[57] The asymmetrical enrichment of SMC is also consistent with a model in which two associated SMC rings independently hold a single DNA duplex and contact each other.[14,52] Wang et al. also proposed a coordinated release of the two rings coupled with the Ter region, beyond which the progression stops.[47]
8. Overall Transition and DNA loading Based on DNA Loop Extrusion

From the viewpoint of protein stability, a recent report has discussed a possible structural transition of the SMC-ScpAB complex.[24] The complex folds into a rod shape capable of tolerating locally unfavorable conformations in the hinge and head regions. That is, the overall structure is maintained by a summation of the stability earned by coiled-coil juxtaposition and the instability at the constrained hinge and the loosened structural region near the ScpA NTD. ATP binding and head-head engagement induces loss of the juxtaposition, which is in turn utilized for relaxation of the hinge domain and the formation of a stable interaction between the ScpA NTD and the ScpB CTD. This explains why in vitro purified SMC-ScpAB complexes have asymmetrical and separated arms.[10,24] However, unfavorable conformations of the ScpA NTD remain in the complexes in *B. subtilis*.[24] (Figure 3C). There might be a mechanism through which the overall structure overrides the negative regulation of ScpB.

Gruber and coworkers have proposed a series of mechanical actions performed by the SMC complex for DNA loading (Figure 5).[19] In their model, the closed-rod form of the complex initially prevents DNA entry by being in a resting conformation, in which the two head domains are separated. Then, the ATP hydrolysis possibly causes the formation of a widely open rod, as an intermediate form just for a short time. Switching between the two modes initiates scanning of specific binding sites within the Spo0J-parS cluster, and catches the DNA loop with the help of basic residues in the hinge domain. During this step, specific binding to Spo0J might prolong the unstable intermediate state. Distinct from the large intra-arm space, Gruber et al. also postulate the presence of another small chamber, which is formed by the SMC head domains and the ScpAB subcomplex for storing two DNA strands of a loop. Alternation between capture and merging results in stepwise additions of DNA strands to the small chamber to produce a growing DNA loop. Structures of the engaged form of the head domain reveal that a C-terminal peptide of the domain reaches across the dimer interface.[24] In this scenario, the peptide could work as a non-return valve for the DNA merging. This proposed mechanism is based on a one-directional loop harvest by the SMC complex, explaining the relative progression by extruding DNA. However, the mechanism that dictates the direction of the loop harvest is not clear yet. If the basic surface of the hinge domain mainly controls capturing DNA strands, the directionality could be explained by the asymmetrical hinge structure with biased basic electrostatic potential. If so, binding of ScpAB might control asymmetrical head-head disengagement, in turn, resulting in biased opening of the rod form of the complex creating the asymmetrical hinge. Despite the elasticity of the arm at the engagement, how the SMC arms would be rigid enough to let DNA strands move by their peristalsis toward the head domain? These questions await answers and should be addressed in the future.

9. Origin of Archaeal SMC Complex

An accurate genome segregation mechanism must operate also in cells belonging to the archaeal domain. Archaeal genomes...
consist of a circular chromosome and possible extrachromosomal elements. Euryarchaeal species contain multiple chromosome copies, and harbor genes for archaeal histone homologs, whereas the crenarchaeal genera contain a single chromosome and lack histone genes. These observations suggest a potential correlation between chromosome copy number and the origin of archaeal histones, which are only found in Euryarchaeota. It is also likely that the archaeal SMC mediates chromosome segregation. Interestingly, smc genes are commonly found in euryarchaeal species, but not in crenarchaeal families characterized to date. This might suggest that SMC is required for maintenance of multiple chromosome copies or individualization of each replication origin. In Crenarchaeota, proteins bearing no sequence homology to bacterial SMC might be responsible for organization and segregation of chromosomes. However, this is a field that awaits investigations, as no information is currently available. Among the euryarchaeal species, however, the locations of genes encoding the two subunit ScpA and ScpB are somehow different from those observed in bacteria. The euryarchaeal scpA, however, is found downstream of smc, and all the annotated cognate scpB genes are distantly located. Therefore, further studies will be required to assess the involvement of ScpB in the archaeal SMC complex. It will also be crucial to understand to what extent the basic mechanisms of condensin-based chromosome organization are shared among archaea. Intuitively, when 30 or more
chromosomes are packed within the small volume of an archaean cell\textsuperscript{[58]} the need for a DNA condensation strategy becomes more stringent.

10. Conclusions and Perspectives
Recent advances in bacterial cytology have elucidated the organization of chromosome domains as well as the positional information of regulatory factors. Hi-C results of the small \textit{Mycoplasma pneumoniae} chromosome (\textasciitilde0.8 Mb) also revealed maintenance of a similar symmetry between the two arms.\textsuperscript{[59]} On the other hand, subsets of proteobacteria, including \textit{Escherichia coli}, do not have SMC. Instead, they encode the MukB protein and its cognate factors MukE and MukF.\textsuperscript{[60–62]} \textit{E. coli} lacks a ParAB partition system and its chromosome is not maintained as juxtaposed as in \textit{B. subtilis}.\textsuperscript{[63]} However, \textit{E. coli} condensin MukBEF with TopoIV promotes timely segregation of newly replicated DNA molecules.\textsuperscript{[64]} Thus, there is no single unified system for chromosome organization and segregation in bacteria.

It is also important to note that the SMC loading phenotype revealed by Hi-C data is highly dependent on Spo0J and parS. However, spo0J mutants do not display severe defects in chromosome segregation as compared to \textit{smc} mutants. Therefore, the growth defect of \textit{smc} mutants is apparently independent of the zipping action itself. Inactivation of any subunit of the SMC complex in \textit{B. subtilis} results in massive accumulation of sister chromosomes interlinked at the replication origin.\textsuperscript{[11,65]} Thus, accurate resolution of new replication origins might be more significant as the main function of the SMC complex. Nonetheless, unlike the abundant protein H-NS that is capable of forming loop,\textsuperscript{[66]} what do SMC proteins recognize in the Spo0J-bound DNA platform? What mechanism does ignite SMC complexes to move along DNA towards the Ter region by dissociation of the preformed specific contacts? Many exciting questions remain to be addressed in the future.

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Conflict of Interest
The authors have declared no conflict of interest.

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