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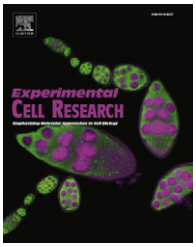

Review Article

Cohesin in determining chromosome architecture

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ABSTRACT

Cells use ring-like structured protein complexes for various tasks in DNA dynamics. The tripartite cohesin ring is particularly suited to determine chromosome architecture, for it is large and dynamic, may acquire different forms, and is involved in several distinct nuclear processes. This review focuses on cohesin's role in structuring chromosomes during mitotic and meiotic cell divisions and during interphase.

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Introduction

Roughly one-fourth of all of our protein-encoding genes code for proteins involved in genome maintenance and cell division, which illustrates the enormous complexity and effort that eukaryotic cells have evolved to divide and faithfully transmit their genomes to the next generation. While many elaborate concepts describing these processes have been formulated and a wealth of

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information has been accumulated about many fundamental events of cell division, there are still huge gaps in our knowledge concerning, for example, chromosome architecture and dynamics.

Even though condensed metaphase chromosomes are known already to school-kids through their textbooks, the layers of structural organization that are required to assemble and partition these chromosomes remain poorly understood. Heterochromatin versus euchromatin, centromeric versus chromosomal arm organization, intergenic versus genic regions, repetitive versus non-repetitive elements, nucleolar or nuclear-envelope-associated regions and many other chromosomal features define chromosome architecture in space and time. It is therefore not surprising that cells have evolved a sophisticated molecular machinery to manage this complex level of organization.

Among the major chromosome organizers is a ubiquitous family of protein complexes based on structural maintenance of chromosomes (SMC) proteins, whose unique structural features make them particularly suited for handling an extensive polymer such as a chromosomal fiber. This was realized quickly after the first description of SMC proteins in 1993 [1], and SMC proteins were subsequently suggested to function as motor proteins, clamps, or crossties that centrally contribute to chromosome structure [2–5]. SMC proteins feature two globular domains at the ends of a ~45 nm long intra-molecular coiled coil that both serve for SMC protein dimerization (Fig. 1A). Specific pairs of SMC proteins form via a high-affinity interaction between the "hinge" domains at one end of the coil "arms". At the same time, the ATPase "head" domains at the other end can dynamically associate and dissociate upon binding and hydrolysis of ATP, respectively [6]. A so-called kleisin protein further connects the two head domains to form a closed ring-like structure (Fig. 1B). This large ring architecture seems ideal to clasp chromosomes inter- or intra-molecularly between the SMC arms in order to tie them up.

The principle of entrapping DNA within a ring is certainly not unique to SMC complexes. A number of proteins that manipulate nucleic acids, including for example replicative helicases such as the MCM licensing factors, RNA helicases such as the Rho transcription terminator, or DNA replication processivity factors such as PCNA or the β-subunit of prokaryotic DNA polymerase III form rings with a six-fold symmetry and a central hole large enough to encompass a double helix (Fig. 1A) [7]. Similarly, DNA mismatch repair proteins like MSH2 and MSH6 can form sliding clamps, i.e. rings that, once they hit a mismatched base-pair, may move further and recruit more clamps [8]. A ring architecture is in general well suited whenever protein complexes need to move along DNA, as rings can – in principle – rapidly slide along nucleic acid strands for long distances without falling off. What makes SMC complexes unique is their ring diameter, which is at least an order of magnitude larger than the rings of the aforementioned complexes, allowing SMCs to topologically encircle not only one DNA helix but two DNA helices, which may even be wrapped around nucleosomes. In this brief review, we discuss how a particular SMC complex named cohesin can exploit this mode of action to determine the architecture of chromosomes and draw parallels to the function of the related condensin, SMC5/6, and prokaryotic SMC complexes that are described in other articles of this special issue.

Cohesin holds sister chromatids together

The cohesin complex was first identified in genetic screens that aimed to identify proteins required for holding together sister chromatids [9,10]. Biochemical and structural studies demonstrated that cohesin's kleisin subunit SCC1 (also named RAD21 or MCD1) simultaneously binds to both head domains of an SMC1/SMC3 heterodimer and to a fourth subunit that is predicted to be largely composed of HEAT-repeat motifs (named SCC3 in yeast and present in two isoforms named SA1 and SA2 in metazoan cells) (Fig. 1B) [11,12]. In germ cells, some of these subunits can be replaced by meiosis-specific versions (see below).

Is there experimental proof that cohesin binds chromosomes by entrapping chromosomes within the ring-shaped structure formed by its SMC1, SMC3, and SCC1 subunits following the principle outlined in the introduction? The findings that (a) opening of the cohesin ring by site-specific proteolytic cleavage of SCC1 or SMC3 is sufficient to release cohesin from chromosomes and to destroy sister chromatid cohesion [13–16], (b) linearization of circular minichromosomes releases their association with cohesin in vitro [17], (c) covalent connection of the interfaces between the

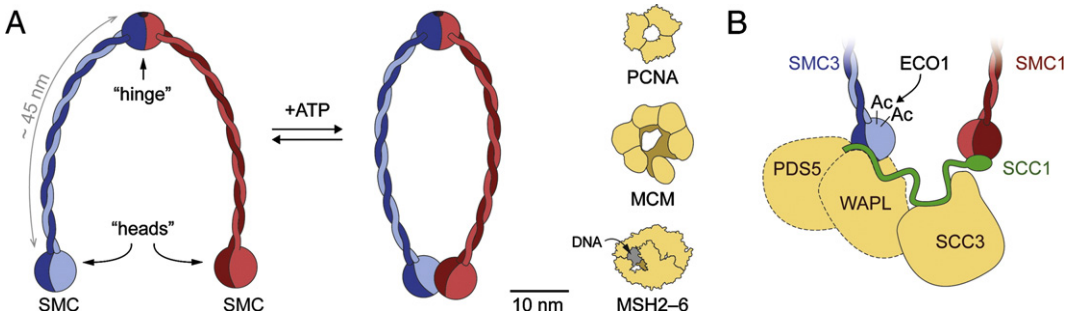

Fig. 1 – Architecture of SMC proteins and the cohesin complex. (A) A ~45 nm long intra-molecular coiled coil separates an ATPase "head", formed by the association of N- and C-terminal globular domains, from a central "hinge" that serves for SMC protein dimerization. Two SMC head domains can associate upon sandwiching two ATP molecules, resulting in a circular SMC architecture with a diameter of 30 nm or more, which is significantly larger than that of other ring-shaped DNA binding protein complexes shown to scale. (B) In cohesin complexes, the kleisin protein SCC1 connects the head domains of an SMC1–SMC3 dimer and recruits the HEAT-repeat containing subunit SCC3. Acetylation of SMC3's head domain by the ECO1 acetyl-transferase counteracts the chromatin-releasing activities of the WAPL–PDS5 complex.

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