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Review

Cohesin: A guardian of genome integrity

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ABSTRACT

Ability to reproduce is one of the hallmark features of all life forms by which new organisms are produced from their progenitors. During this process each cell duplicates its genome and passes a copy of its genome to the daughter cells along with the cellular matrix. Unlike bacteria, in eukaryotes there is a definite time gap between when the genome is duplicated and when it is physically separated. Therefore, for precise halving of the duplicated genome into two, it is required that each pair of duplicated chromosomes, termed sister chromatids, should be paired together in a binary fashion from the moment they are generated. This pairing function between the duplicated genome is primarily provided by a multimeric protein complex, called cohesin. Thus, genome integrity largely depends on cohesin as it ensures faithful chromosome segregation by holding the sister chromatids glued together from S phase to anaphase. In this review, we have discussed the life cycle of cohesin during both mitotic and meiotic cell divisions including the structure and architecture of cohesin complex, relevance of cohesin associated proteins, mechanism of cohesin loading onto the chromatin, cohesion establishment and the mechanism of cohesin disassembly during anaphase to separate the sister chromatids. We have also focused on the role of posttranslational modifications in cohesin biology. For better understanding of the complexity of the cohesin regulatory network to the readers, we have presented an interactome profiling of cohesin core subunits in budding yeast during mitosis and meiosis.

1. Introduction

Mitosis and meiosis are the eukaryotic cell division processes, either of which takes place for the generation of daughter cells of equal or half the ploidy levels, respectively of the progenitor mother cell. During these cell division processes, chromosomes, following DNA replication, align at a position equidistant from the two spindle poles following their bi-polar attachment to the microtubules emanating from those spindle poles. The segregation of the chromosomes is then achieved due to the pulling forces exerted by the microtubules (spindles). In eukaryotic cell division replication of DNA and segregation of chromosomes are temporally separated. Therefore, it is extremely essential to keep the sister chromatids together from the time of their generation during S phase till the time they split asunder during metaphase to anaphase transition. The molecular glue which keeps the sister chromatids together from S phase to metaphase to anaphase transition is known as “cohesin”, a multiprotein complex, which is believed to entrap the sister chromatids in its tri-partite ring structure [1]. The spatiotemporal regulation of the association and dissociation of the cohesin complex to and from the sister chromatids, respectively is instrumental in faithful segregation of the sister chromatids during both mitosis and meiosis. Therefore, in this review, we wish to accommodate literature from various studies on how cohesin interacts with the chromatin and generates sister chromatid cohesion (SCC) and how it dissociates timely to pave the way for faithful segregation of genome from one generation to the next.

The cohesin complex plays a fundamental role in holding sister chromatids together during mitosis and meiosis across eukaryotes. Apart from this canonical role during cell division, recent developments in the field have shown the role of cohesin in many other cell division-independent cellular processes like transcriptional regulation, DNA repair, chromosome condensation which are discussed elsewhere [2–7]. Any discrepancies in the functions of cohesin result either in aneuploidy leading to tumorigenesis, spontaneous miscarriages, still birth, Down's syndrome or in severe developmental defects like Cornelia de Lange Syndrome, Roberts syndrome or Warsaw Breakage Syndrome. Recently, the importance of cohesin function to human health has been acknowledged by coining a term, called “Cohesinopathies” to describe the effect of mutation in cohesin machineries in human (reviewed in [8,9]; [10]).

Few decades earlier when several research groups were trying to address the mechanism of SCC, two views emerged. One, cohesin may be generated through active participation of some protein factors. Second, cohesion may be a legacy of DNA replication automatically formed due to catenation of the sister chromatids with each other [11] (reviewed in [12]). The latter one needs the action of topoisomerase to resolve the intertwined sister chromatids for their

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separation during anaphase [13]. Experimental evidence suggests that catenations can indeed mediate some cohesion between sister chromatids in the absence of topoisomerase activity [14,15]. However, identification of several proteins involved directly in generation of SCC has highlighted firmly that the act of cohesion is primarily protein mediated [16–18].

Over the last two decades, advancements in the field of molecular biology, cell biology and computational biology along with the aid of sophisticated biochemical and microscopic techniques have successfully surmounted the limitations of visualizing the chromosomes, centromeres, cellular organelles and proteins even for organisms like yeasts with very small neuclei. As a result, a drastic enrichment in the information regarding chromosome biology has been observed in the past few years and the wealth of information is getting almost doubled in every few years. Thus it has become prerogative to review such a vibrant field at a regular intervals. In this review, we have discussed the life cycle of cohesin in the context of its timely regulated loading on the chromatin, establishment of cohesion, the mechanism of holding sister chromatids, its maintenance and dissociation from chromosomes during mitosis and meiosis, with special emphasis on *Saccharomyces cerevisiae*. Occasionally, we have compared budding yeast cohesin/cohesion mechanism with that in other model eukaryotes. To understand the complexity of the cohesin regulatory network during mitosis and meiosis, we have provided a manually curated interactome table (Table 1) for all the four core subunits of cohesin (Smc1, Smc3, Mcd1 (Rec8) and Irr1) in budding yeast based on the available literature retrieved from BioGrid3.1. It has also been noted that posttranslational modifications (PTMs) of cohesin and its related proteins play an important role in regulation of cohesin functions in different organisms and within the same organism in different cell types. We have accommodated all different types of PTMs of cohesin and its associated proteins found in different organisms with respect to their function in a compiled table (Table 2). At the end, we have presented evidence of cohesin like proteins in bacteria to emphasize that proteins involved in tying up different chromosomal locales may be a generalized adopted theme. We also encourage readers to refer to the recent reviews published elsewhere for further understanding the biology of cohesin [19–21].

2. Architecture of the cohesin core complex and its associated proteins

Cohesin complex comprises of four core subunits which are conserved from yeast to mammals. In budding yeast, mitotic cohesin complex comprises of four subunits: Smc1, Smc3, Scc1/Mcd1 and Scc3 whereas in meiotic cohesin complex Scc1 is replaced with Rec8 (Fig. 1A) (reviewed in [21,22]). The structural organization of individual components within the cohesin complex has been well characterized in budding yeast [23,24]. The cohesin complex also shows structural resemblance with cohesin from other species on the basis of the sequence conservation among the subunits, biochemical and electron microscopic observations [25–27]. Out of the four subunits, Smc1 and Smc3 are the members of the “structural maintenance of chromosomes” (SMC) family which are large ATPases with an unusual domain organization [16,28]. During the folding process, the N- and C-termini of the individual polypeptide chains of SMC proteins come close to each other upon bending on the central ‘hinge’ domain forming a globular ATPase ‘head’ domain. This folding generates 40 nm long anti-parallel coiled-coil structures (Fig. 1A) [23,29,30]. The hinge domains of Smc1 and Smc3 remain tightly associated with each other whereas the ATPase heads of both the proteins are physically connected by the Scc1/Mcd1/Rad21 subunit [23] to complete a tripartite ring structure. Scc1/Mcd1/Rad21 is a member of ‘kleisin’ (Greek word for ‘closure’) family of proteins as it bridges the ATPase head domains of Smc1 and Smc3 subunits [31]. The N terminus of Scc1/Mcd1/Rad21 binds to the ATPase domain of Smc3 whereas the C-terminus binds to the ATPase domain of Smc1. Thus, Smc1 and Smc3 bind to each other at one end *via* their hinge domains and at the other end with the help of Scc1/Mcd1/Rad21 *via* their ATPase domains to form the ring like structure with an outer diameter of ~40 nm [23]. This organization of cohesin subunits has been well supported by electron microscopic data of purified vertebrate cohesin complexes [27] and by crystal structures of subcomplexes of cohesin or related SMC complexes [23,24]. ATP binding to the ATPase heads of Smc1 and Smc3 is essential for association of Scc1/Mcd1/Rad21 with the Smc1 and Smc3 heterodimer [32,33]. The fourth subunit of core cohesin complex, Scc3, is associated with Scc1 [34]. The sequence of this subunit contains HEAT repeats, responsible for protein–protein interactions [35]. The structural/functional roles of Scc3 and its HEAT repeats remain poorly understood till date. In vertebrate somatic cells, two closely related Scc3 homologs are present, known as stromalin antigens 1 and 2 (SA1 and SA2). These cells contain cohesin complex having either of these two Scc3 homologs, but never both at a time (Fig. 1B) [26,36]. In the same cells, cohesin SA2 is about threefold more enriched than cohesin SA1, whereas in *Xenopus* eggs, cohesin SA1 is about ten times more abundant than cohesin SA2. The functional difference between cohesin SA1 and cohesin SA2 was recently addressed by Losada and colleagues. They have reported that SA1 containing cohesin complex is involved in gene regulation and replication of telomeres whereas SA2 containing cohesin is mainly responsible for sister chromatid cohesion [37,38].

It has been observed in many organisms that meiotic cohesin complex is different from the mitotic cohesin complex. In meiosis, the mitotic kleisin subunit Scc1/Mcd1/Rad21 is substituted by a meiosis-specific paralog called Rec8 [17,39]. The biological significance of this substitution is as follows. In mitosis all the cohesin, at least in budding yeast, is removed from the chromatin in one step during metaphase to anaphase transition by the proteolytic cleavage of its Scc1 subunit by a protease called separase. However, in meiosis, cohesin removal from the chromosomes takes place in a step wise manner. During metaphase I to anaphase I transition, only Rec8 subunit of arm cohesin is cleaved by separase but that of centromeric and pericentromeric cohesin remains protected which becomes degraded by the same separase during metaphase II to anaphase II transition. This stepwise removal of cohesin depends on Rec8 but not on Scc1/Mcd1/Rad21. Rec8 orthologs have been subsequently discovered and characterized in many species [40] (reviewed in [41]), including *Drosophila*, where a Rec8-related protein C(2)M also expresses during meiosis [42]. However, it is yet to be clarified whether C(2)M has a similar role as Rec8, since C(2)M inactivation causes less severe defects in *Drosophila* gametogenesis than Rec8 deletion in yeast meiotic cells. This could be due to the fact that *Drosophila*, like many other organisms including mammals, also expresses Scc1/Mcd1/Rad21 at low levels in meiosis (reviewed in [43]) and partial functional redundancy may exist between C(2)M and Scc1/Mcd1/Rad21. Interestingly, it has been shown that even more distantly related proteins might functionally replace Rec8. For example, ORD protein from *Drosophila*, which is functionally more similar to Rec8 than C(2)M, but differs in sequence from kleisins or Rec8 [44–46]. Other cohesin core subunits also possess their meiotic isoforms. In mammals, Smc1β and STAG3 replace Smc1 and SA1/SA2, respectively [47–50] and in fission yeast Scc3 ortholog Psc3 exists along with a related protein, named Rec11 in the meiotic cells [51]. Recently a new mammalian cohesin subunit, Rad21-like protein (Rad21L) has been identified in mouse which has a sequence similarity both with Rad21 and Rec8 [52,53]. During early meiotic prophase, Rad21L localizes along axial elements or lateral elements of the synoptonemal complex in a way which is mutually exclusive of the manner of Rec8 deposition on not-yet-synapsed homologs, implying that Rad21L may be involved in pairing of homologous chromosomes. Interesting, it has been demonstrated that although majority of Rad21L is dissociated by the end of pachytene, a small fraction still persists at the centromere till metaphase I