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SMC (STRUCTURAL MAINTENANCE OF CHROMOSOME) PROTEINS: REVIEW ARTICLE

[1] *Sasikanth Kommu,* [2]*Mahesh Chandra Sharma,* [3]*Anjali Padhiar,* [4]*Falguni Patel,* [5]*Jyotsna Tyagi*

Abstract:

Structural maintenance of chromosome (SMC) proteins, along with other non SMC elements (Nse) form specific complexes that organize, stabilize, segregate and repair chromosomes. The proper segregation of genetic material during cell division is very vital since defects in the chromosomal DNA segregation may lead to several chromosomal aberrations some of which are lethal. In eukaryotes Cohesin is a ring shaped protein complex, formed by SMC1/3 hetero dimmer. It is required for sister chromatid cohesion and proper positioning of mitotic spindle. Condensin, a complex comprising of SMC2/4 hetero dimer organizes the chromosomes in eukaryotes and helps in their segregation in to daughter cells. Eukaryotic SMC5/6 complex is relatively less studied and is found to have a role in DNA repair though the precise mechanism is not yet understood completely. Prokaryotic SMC proteins have a related though not identical function with their eukaryotic counterparts.

Keywords: *SMC proteins, condensisn, cohesion, Non SMC proteins, Kleisins*

1. INTRODUCTION

The genetic material of all living organisms is DNA. In eukaryotes within the nucleus DNA forms a reticulate network, known as chromatin. This network condenses to form short structures known as chromosomes that are involved in processes such as replication, segregation and repair (Losada & Hirano, 2005). How the reticulate network of chromatin condensed into short chromosomes was an unanswered question for a long time. The DNA replicates during synthesis (S) phase of cell cycle and is equally distributed to the daughter cells during anaphase. However, the replicated DNA in the form of chromosomes remains together until the cell transits from metaphase to anaphase, during which they split and migrate to different poles. What tethers them and what releases them in anaphase was an unanswered question for a long time. However, the discovery of Structural Maintenance of Chromosome proteins has provided some clues to these unanswered questions (Losada & Hirano, 2005; Jessberger, 2002; Uhlmann, 2004).

2. SMC PROTEINS

SMC proteins were first observed in a mutant Escherichia coli with impaired chromosome segregation. These SMC proteins are seen in all living organisms (Cobbe & Heck, 2004). In majority of the prokaryotes and archea a single SMC protein that forms a homo dimer is seen (Hiraga, 2000). However in eukaryotes at least six SMC proteins SMC1-6 are seen. These proteins form specific hetero dimers namely SMC1/3,

[1,2,3,4,5] *Department of Biotechnology, Kadi Sarva Vishwavidyalaya, Sector -23, Gandhinagar, Gujarat, India.*

SMC2/4 and SMC 5/6. Each of these specific dimers associate with non structural maintenance of chromosome elements (Nse) to form large protein complexes that have specific functions in the cohesion, condensation and repair of DNA (Haering & Nasmyth, 2003; Hirano, 2005; Lehman,2005).

3. SMC HETERO DIMERS

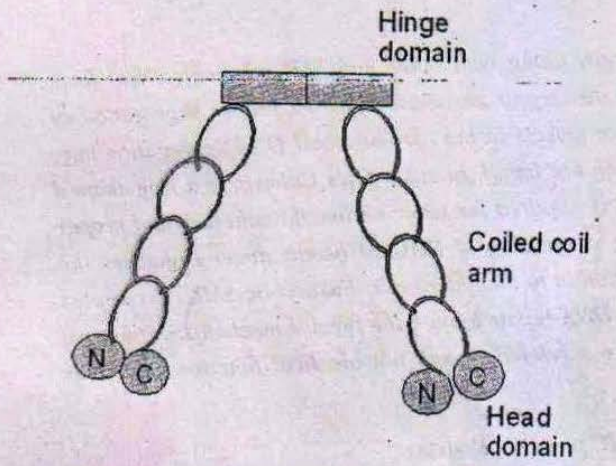

Figure1 corresponds to SMC dimer. The monomers are joined at hinge domain where as their head domains are free. These proteins have coiled coil interactions that give them a rod shape (N amino terminus, C carboxyl terminus).

The SMC proteins exhibit antiparallel coiled coil interactions which give them a rod like appearance. As shown in figure 1 these proteins have a head domain and a hinge domain. The head domain is formed by the amino and carboxyl termini, and ATP binds to the head domain. The hinge domain has a site where the SMC monomers attach to form a V shaped hetero dimer. The SMC hetero dimers associate with certain non SMC proteins to form multi-subunit complexes, the functional unit of the SMC proteins (Nasmyth & Haering, 2005).4. Kleisins

Kleisins are a super family of non SMC proteins that interact with SMC proteins to form a closed ring-like structure. Eukaryotic kleisins are divided into alpha, beta, gamma and delta classes. Alpha kleisins are represented by Scc1 and Rec8 (Meiotic Recombination protein) in budding yeast, and are associated with SMC1/3 hetero dimer. Beta kleisins are represented by Kle-2 (Kleisin-2) in worms and gamma kleisins are represented by XCAP-H (Xenopus chromosomal ATPase H subunit) in frogs, and Barren in flies SMC2/4 hetero dimers associate with either beta kleisins or gamma kleisins but never both. Delta kleisins are represented by Nse4 in budding yeast and are associated with the SMC5/6 hetero dimer (Nasmyth & Haering, 2005). ScpA represents the prokaryotic kleisins (Losado and Hirano,2005).

5. SMC1/3 PROTEIN COMPLEX- COHESIN

The V shaped SMC1/3 hetero dimer is linked by Scc1, an alpha kleisin, to form a tripartite ring that holds replicated sister chromatids by encircling them. Scc3, Nse is linked to Scc1. This protein complex is shown in figure 2, and is known as cohesin complex. Cohesin complex seen along inter chromatid axis, holds the replicated sister chromatids until anaphase. This association of replicated chromosomes till anaphase is called sister chromatid cohesion (Lee & Orr-Weaver, 2001). The cohesion of sister chromatids helps the mitotic spindle to recognize and segregate the replicated chromosomes to different poles. At anaphase a protease called separase is activated and cleaves the alpha kleisin, Scc1, thereby opening the cohesin ring and releasing the sister chromatids, as shown in figure 3 (Uhlmann, 2001). In response to a DNA double strand break the cohesin is recruited on to the chromosome to repair the DNA damage during replication and even after replication (Strom et al 2004; Strom and Sjogren, 2005).

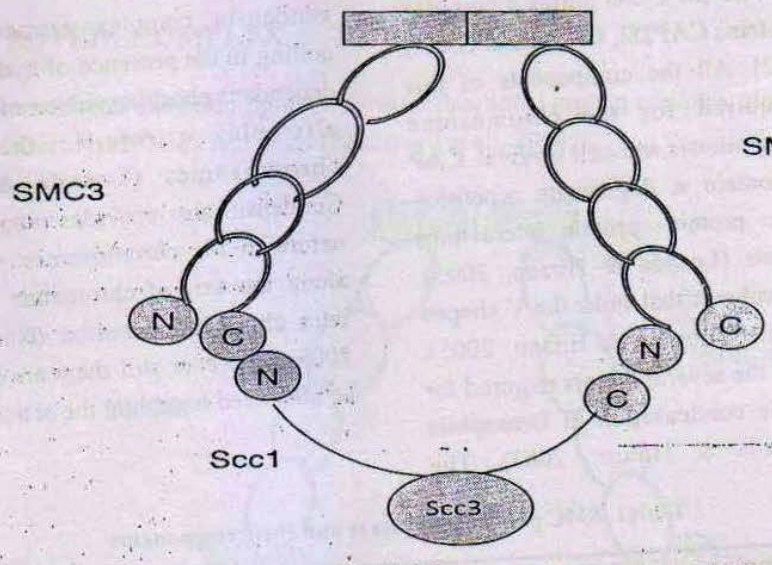

Figure3 showing the structure of cohesin complex in which SMC1 &3 heterodimer is linked by alpha kleisin, Scc1. Scc3 is a Nse linked to Scc1 (N amino terminus, C carboxyl terminus).

6. SMC2/4 PROTEIN COMPLEX- CONDENSIN

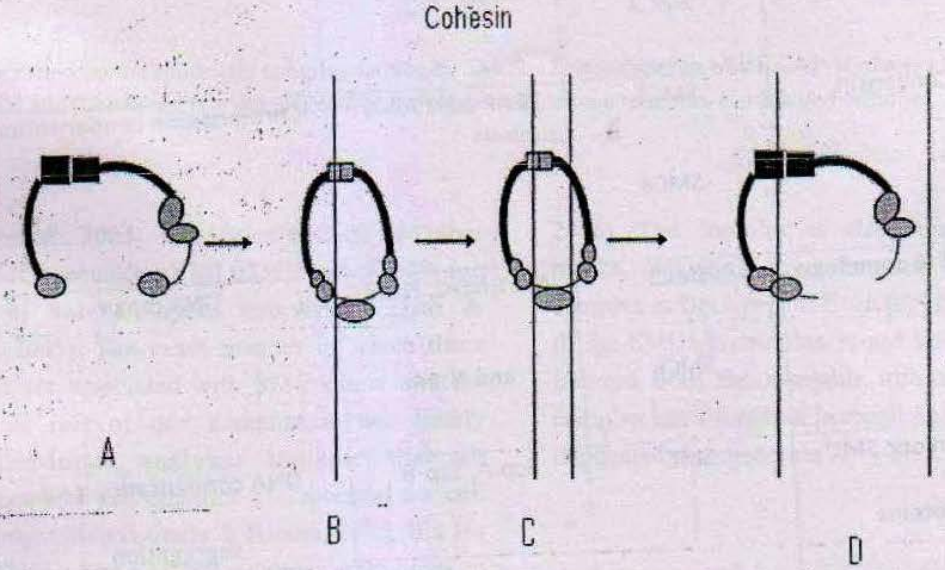

Figure4 showing the ring model proposed to explain the action of cohesin. The cohesin encircles DNA by forming a tripartite ring. Linkage is established between replicated DNA by an unknown mechanism. During the transition from metaphase to anaphase the Scc1 subunit of cohesin is cleaved by separase and the sister chromatids are released (A- loading of cohesin onto DNA, B- cohesin seen around un replicated DNA, C- cohesin seen around replicated DNA & D- separation of cohesin and release of DNA).

SMC 2 and SMC4 hetero dimer forms a complex with non SMC proteins CAPD2, CAPG and CAPH (Jesserbergh, 2002). All the components of this complex are required for the chromosome condensation during mitosis and cell survival. CAP D2 and CAPG contain a degenerate repetition motifs involved in protein- protein interactions called HEAT repeats (Losada & Hirano, 2005). CAPH is a kleisin subunit that links the V shaped SMC2-4 hetero dimer (Losada & Hirano, 2005). Condensin is one of the several factors required for in vivo chromosome condensation in Drosophila melanogoster (Losada & Hirano, 2005). The condensin complex introduces positive super coiling in the presence of hydrolysable ATP. Cdk-1 dependant phosphorylation of non SMC units may also play a role in the condensation of chromosomes (Losada & Hirano, 2005). Condensin also provides proper shape and elastic nature to the chromosomes. Condensin is found along the axis of chromatids is also required for intra chromatid cohesion (Nasmythy & Haering, 2005). However still there are several questions to be answered regarding the action of condensin.

Table1. SMC protein complexes and their components

Protein complex	SMC components	Non-SMC components	Function of protein complex
Cohesin	SMC1 SMC3	Scc1/Rad21	Sister chromatid cohesion
Condensin	SMC2 SMC4	CAP D2, CAP-G	Chromosome condensation
SMC5/6 complex	SMC5 SMC6	Nse1,Nse2, Nse3 and Nse4	DNA repair
Prokaryotic SMC proteins	SMC	Scp-A, Scp-B	DNA condensation and segregation

Table1 showing various SMC protein complexes, their components and their function.

7. SMC5/6 PROTEIN COMPLEX

The SMC5/6 hetero dimer shown in figure 4, forms a functional protein complex along with at least four non SMC proteins; Nse1, Nse2, Nse3 and Nse4 (Pebernard et al., 2004;

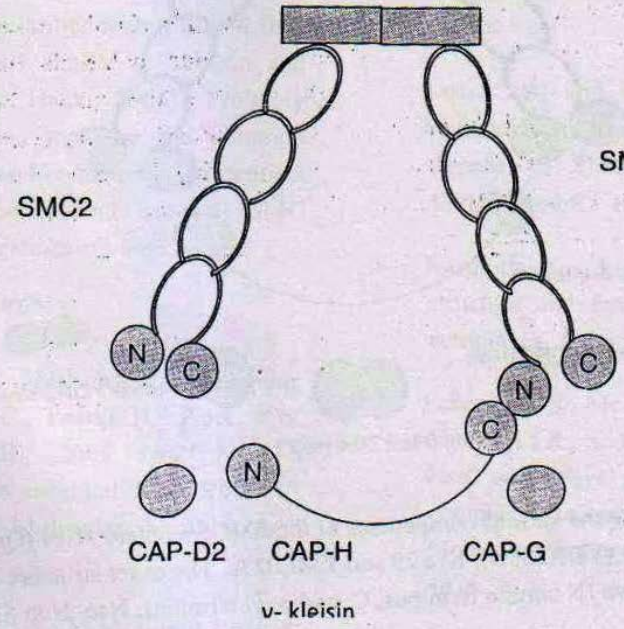

Figure5 showing the condensin complex formed by SMC2/4 hetero dimer to which CAP-H, the γ- kleisin is bound. CAP-D2 and CAP-G are Nse components of the complex (N amino terminus, C carboxyl terminus, Nse- Non SMC element).

Bin Hu et al.., 2005). In addition to these two other non SMC subunits -YML023C and Kre29 are found in Saccharomyces cerevisiae (Zhao & Blobel, 2005). The exact manner in which these subunits are associated with SMC dimer and the functional role of this complex is not clearly known. Mutant analyses indicate that all components of this complex are essential for cell cycle progression (Losada & Hirano, 2005; Bin Hu et al.., 2005). The SMC5/6 complex only binds to the replicated chromosomes, i.e. to chromosomes during S and G2 phases (Betts Lindroos et al., 2006). The complex is also recruited to DNA breaks, indicating direct function of the SMC5/6 complex in DNA repair. Even though the exact role of the SMC5/6 complex is not known, it may be inferred from the available information that this complex has a function in repair and segregation of duplicated chromosomes.

8. Bacterial SMC proteins

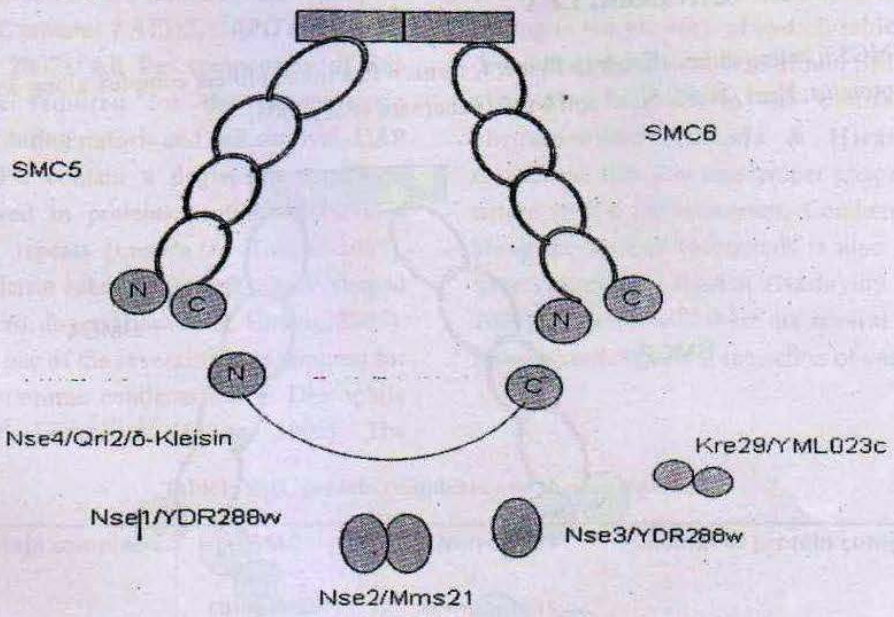

Figure6 showing the various components of the SMC5/6 hetero Nse4 (Qri2), Nse1, Nse2 (Mms21), Nse3 (YDR288w), Kre 29 and YML023c. The exact structure of this complex is still unknown (N amino terminus, C carboxyl terminus, Nse- Non SMC element).

There are several similarities between the segregation machineries of prokaryotes and eukaryotes (Losada & Hirano, 2005). Mutant analysis in Bacillus subtilis has shown that Smc gene is responsible for condensation and segregation of bacterial chromosome. The SMC proteins of bacteria have a related, if not identical function with their eukaryotic counter parts in vivo (Losada & Hirano, 2005).

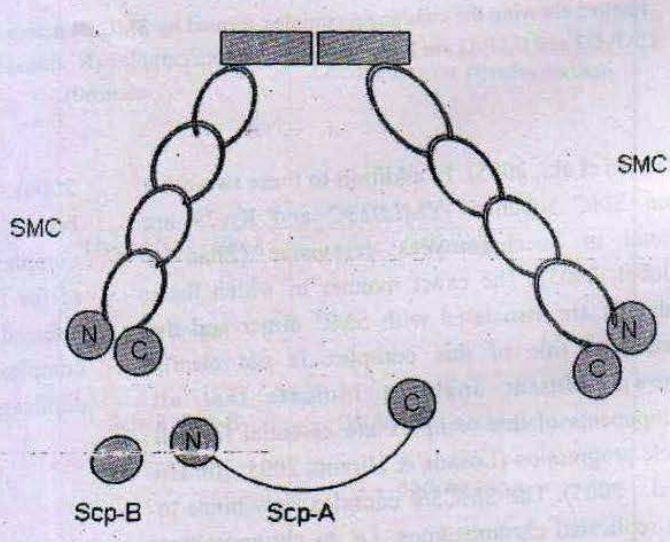

Figure7 showing bacterial SMC homo dimer proteins, Scp-A, the kleisin subunit and Scp-B. The exact structure of this complex is still unknown (N amino terminus, C carboxyl terminus, Nse- Non SMC element).

ScpA is a prokaryotic kleisin that links SMC homo dimers and Scp B binds to Scp A. This SMC-ScpA-ScpB complex pulls the replicated DNA to the opposite poles probably by DNA super coiling (Losado & Hirano, 2005). The bacterial SMC proteins have great similarities with SMC1-4 than SMC5&6 and functions similar to cohesin and condensin (Cobbe & Heck, 2004). Probably bacterial SMC proteins may be the common ancestors of cohesins and condensins. To confirm this and to know more about bacterial SMC proteins further investigations are necessary.9.

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