

# Sister Chromatid Cohesion Control and Aneuploidy

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## Key Words

Aneuploidy · Chromosome segregation · Cohesin · Cohesinopathies · Cohesin-regulators · Sister chromatid cohesion

## Abstract

Apart from a personal tragedy, could Down syndrome, cancer and infertility possibly have something in common? Are there links between a syndrome with physical and mental problems, a tumor growing out of control and the incapability to reproduce? These questions can be answered if we look at the biological functions of a protein complex, named cohesin, which is the main protagonist in the regulation of sister chromatid cohesion during chromosome segregation in cell division. The establishment, maintenance and removal of sister chromatid cohesion is one of the most fascinating and dangerous processes in the life of a cell. Errors in the control of sister chromatid cohesion frequently lead to cell death or aneuploidy. Recent results showed that cohesins also have important functions in non-dividing cells, revealing new, unexplored roles for these proteins in human syndromes, currently known as cohesinopathies. In the last 10 years, we have improved our understanding of the molecu-

lar mechanisms of the cohesin and cohesin-interacting proteins regulating the different events of sister chromatid cohesion during cell division in mitosis and meiosis.

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During cell division, the pair of recently synthesized DNA molecules, now called sister chromatids, remain in close proximity until the precise moment of segregation during the metaphase/anaphase transition. Sister chromatid cohesion is regulated by cohesin, a multiprotein complex, which was characterized in *Saccharomyces* and *Xenopus* [Guacci et al., 1997; Michaelis et al., 1997; Losada et al., 1998]. This complex is essentially composed of 4 core subunits: 2 evolutionarily very conserved proteins that belong to the structural maintenance of chromosomes family of proteins (SMC1 and SMC3), 1 kleisin  $\alpha$  (from the Greek for closure) subunit SCC1/RAD21 and stromalin SCC3/SA/STAG (fig. 1A). Vertebrates have 2 mitotic SCC3/SA/STAG members, SA1/STAG1 and SA2/STAG2 [Carramolino et al., 1997], which do not coexist and are present in different cohesin complexes in *Xenopus* [Losada et al., 1998] and human [Sumara et al., 2000]. In germ cells, distinct meiosis-specific subunits have

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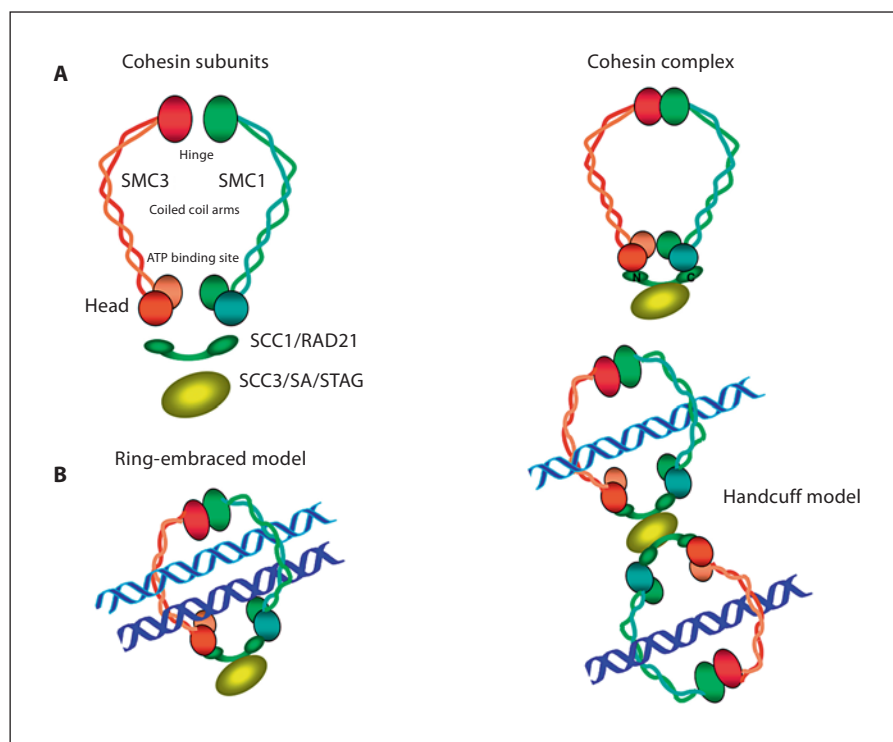
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1424–8581/11/1334–0223\$38.00/0

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**Fig. 1.** Structural model of cohesin complexes. **A** Cohesin subunits and ring-like structure for cohesin complexes. A heterodimer shaped by the interactions of the hinge regions from SMC1 and SMC3 form the ring arrangement. The N- and C-termini regions of SCC1/RAD21 kleisin subunit interact with the head domains from SMC3 and SMC1, respectively, closing the ring. The SCC3/SA/STAG subunit interacts with kleisin, maintaining the ring-like structure. **B** Two proposed models, by which cohesin complex mediates sister chromatid cohesion. In the ring-embraced model, a single cohesin ring hugs 2 sister chromatids. The handcuff model presupposes that the cohesin ring may encircle a single chromatid and interacts with a second ring that embraces the other sister chromatid. The interaction between these 2 cohesin rings is mediated by a single SCC3 molecule.



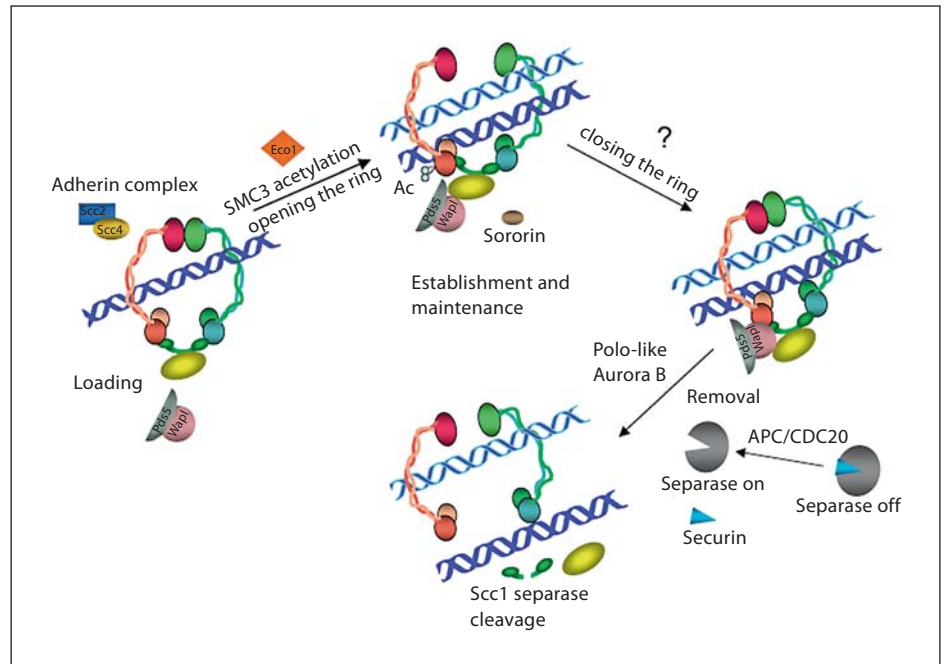
been characterized in various organisms. In mammals, the meiotic paralogues of SMC1, SCC1/RAD21 and SA/STAG1/2 are thus SMC1 $\beta$  [Revenkova et al., 2001], REC8 [Parisi et al., 1999; Watanabe and Nurse, 1999] and STAG3 [Pezzi et al., 2000; Prieto et al., 2001], respectively. Based on the electronic microscopy results and structural characteristics of SMCs, it was proposed that these complexes form a ring-like structure (fig. 1A) and mediate cohesion by embracing chromatin fibers from the 2 sister chromatids (embraced model in fig. 1B) [Gruber et al., 2003] and/or by the 2-ring handcuff model, in which each sister chromatid is encircled by 1 cohesin ring and the 2 cohesin rings associate by SCC3/STAG-dependent interactions (fig. 1B) [Zhang N et al., 2008b]. These 2 models are not mutually exclusive.

On the other hand, now we know that most aneuploidies derive from errors in maternal meiosis and that maternal age is a risk factor for human trisomies [Hassold and Hunt, 2001]. Meiosis is characterized by a single round of DNA replication, followed by 2 rounds of chromosome segregation, to yield haploid gametes from diploid germ cells. Control of sister chromatid cohesion presents important differences between mitotic and meiotic cell cycles, which will be discussed in this present review.

In addition to their canonical role as 'chromosome glue' during cell division, cohesins are involved in additional cellular mechanisms including centromeric heterochromatin formation, post-replicative double-strand break repair, centrosome dynamic, and transcription control. This review illustrates the general features and more relevant molecules involved in the regulation of sister chromatid cohesion during chromosome segregation and the relationships with aneuploidy and other cohesinopathies.

### Regulation of Loading, Establishment, Maintenance and Removal of Cohesin Complexes during Chromosome Segregation

Failures in chromosome segregation during mitosis lead to aneuploidy, which is a frequent feature of tumor development. The control of chromosome segregation is managed by a complex network of events, which guarantees that each daughter cell receives the right chromosome number. One of the best regulated processes in this network is the association/dissociation of sister chromatids. In *Saccharomyces cerevisiae* mitosis, the cohesin complexes are loaded near G1 to S phase, but, in most or-



**Fig. 2.** Cohesin-interacting proteins controlling the different steps of sister chromatid cohesion. The adherin complex formed by SCC2 and SCC4 proteins is involved in the loading of cohesin complex to chromatin. ECO1-dependent SMC3 acetylation regulates the opening of cohesin ring allowing de novo synthesized chromatid to enter through the cohesin complex. The molecular mechanism closing the cohesion ring again is currently unknown, but it has been proposed that this process is dependent of the PDS5/WAPL complex. Sororin is a protein needed for the main-

tenance of cohesion; however, this specific function has not been determined yet. Removal of chromatid cohesion is mediated by Aurora B and Polo-like kinases and by the specific protease separase. Separase and its inhibitor securin are forming a complex until APC/CDC20 ubiquitinizes securin, which is released from the complex and degraded by proteasome. Separase is now activated to cleave the SCC1 kleisin subunit removing cohesins from chromosomes.

organisms studied, cohesins bind to chromatin in telophase [Nasmyth, 2001]. The loading of cohesin complexes to chromosomes depends on the Scc2/Scc4 adherin complex [Ciosk et al., 2000; Watrin et al., 2006] (fig. 2). This loading is not sufficient for the cohesion function in chromosome segregation and the Eco1/Ctf7p acetyltransferase is required for the establishment of cohesion [Skibbens et al., 1999; Toth et al., 1999]. A substrate of Eco1 acetylase is SMC3 and this cohesin subunit is acetylated in an Eco1-dependent manner during replication to promote sister chromatid cohesion [Ben-Shahar et al., 2008; Zhang J et al., 2008a] (fig. 2). Human SMC3 is acetylated at K105 and K106 by the human Eco1 homolog ESCO1; these acetylation sites are located in the middle of the N-terminal head domain, which contains the 'Walker A' nucleotide-binding domain and it could be important in the interactions of SMC1/SMC3 heterodimer with SCC1 for closing the ring. Very recently, Heidinger-Pauli et al. [2010], using SMC mutants proteins to block steps in co-

hesin's ATPase cycle in yeast, developed a working model showing how SMC3 binding to ATP might modulate cohesin binding and cohesion establishment and help us understand the role of this cohesin-cofactor.

Two cohesin-regulators Rad61/WapL and Pds5 are also involved in the opening/closing of cohesin ring by interactions with different cohesin subunits [Rowland et al., 2009] (fig. 2). These cofactors are necessary for cohesin complex dynamics, but are not considered components of the canonical cohesin complex. One of these cofactors is PDS5/BimD/Spo76 [Denison et al., 1993], which interacts with human SA1/STAG1- and SA2/STAG2-containing complexes in somatic cells [Sumara et al., 2000]. Two vertebrate PDS5 proteins, PDS5A and PDS5B, have been characterized [Losada et al., 2005]. PDS5 are large HEAT-repeat proteins that bind to chromatin in a cohesin-dependent manner in both human cells and *Xenopus* egg extracts. They are not required for cohesin association to chromosomes, but are needed for maintaining co-

hesion. RNAi depletion of PDS5A and/or PDS5B in HeLa cells provokes partial defects in sister chromatid cohesion and preferentially alters centromeric cohesion in *Xenopus* egg extracts. These chromosomes contain unusually high levels of cohesins, suggesting a role for PDS5 proteins in the regulation of cohesin-mediated cohesion in vertebrate mitosis. Mice lacking *Pds5B* function die shortly after birth and exhibit multiple developmental anomalies that resemble those found in humans with Cornelia de Lange syndrome, indicating a relevant function for PDS5B beyond chromosome segregation [Zhang et al., 2007]. To date, however, there are no known studies of the putative role of PDS5 proteins in sister chromatid cohesion and chromosome dynamics during mammalian meiosis.

Another interesting cohesin cofactor is the product of the previously identified *Drosophila wings apart-like* (*Wapl*) gene, involved in heterochromatin organization [Verni et al., 2000]. Human WAPL regulates the resolution of sister chromatid cohesion and promotes cohesin complex removal by direct interaction with the RAD21 and SA/STAG cohesin subunits [Gandhi et al., 2006; Kueng et al., 2006]. *Wapl* was found on AE/LE in some prophase I stages in mouse spermatocytes [Kuroda et al., 2005] and oocytes [Zhang et al., 2008b], colocalizing with SYCP3; however, no more extensive study has been carried out on the role of *Wapl* in meiosis. Further cytological and biochemical studies are needed to characterize the role of *Pds5* and *Wapl* during meiosis.

Sororin is a protein which has been implicated in centromere cohesion. Sororin was identified in a screen for substrates of anaphase-promoting complex (APC) in vertebrates for the first time, and, to date, no homologues have been described in other organisms [Rankin et al., 2005]. Different results in somatic cells suggested that sororin interacts with the cohesin complex and it is essential for the maintenance of sister chromatid cohesion (fig. 2). Sororin is ubiquitinated and degraded after sister chromatid cohesion is dissolved [Rankin, 2005]. Studies on sororin-depleted and shugoshin-depleted cells indicated that sororin and shugoshin might act in concert in the protection of centromeric cohesion [Díaz-Martínez et al., 2007]. More recently, Schmitz et al. [2007] reported that sororin is also needed for efficient repair of DNA double-strand breaks in G2 and for maintaining stable chromatin-bound cohesin in G2, suggesting a crucial cohesin regulator role for this protein.

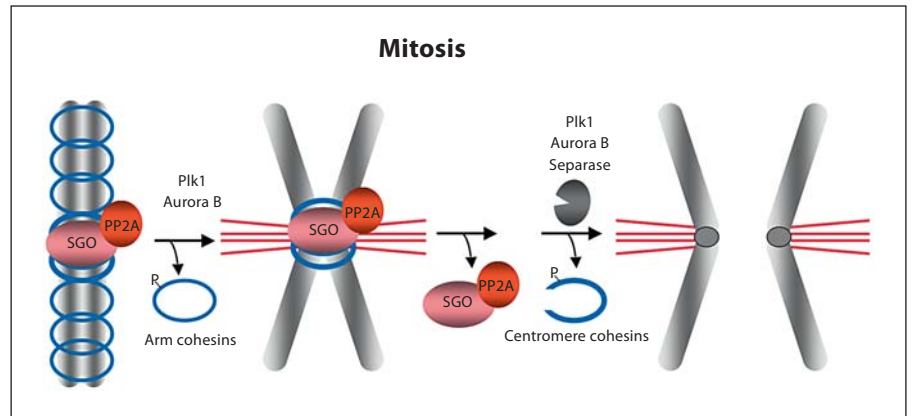
The release of cohesin complexes from chromatin at the metaphase/anaphase transition is mediated by separase, a specific cysteine protease, that cleaves the SCC1

subunit of the cohesin complex, destabilizing cohesion and allowing chromatid segregation [Uhlmann et al., 1999] (fig. 2). Before anaphase, separase remains inactivated by binding to its specific inhibitor securin [Ciosk et al., 1998]. In metazoa, dissociation of cohesin complexes from chromatin proceeds in a 2-step manner. In a first step, the bulk of cohesin complexes is removed from chromosome arms during prophase by a separase-independent pathway [Waizenegger et al., 2000], in which phosphorylation of the SA2/STAG2 subunit by Aurora B and Polo-like kinases triggers the removal of arm cohesins [Hauf et al., 2005]. Cohesin complexes remain essentially at centromeres until the chromosomes are correctly bi-oriented and the spindle assembly checkpoint is completed in metaphase. Activation of the anaphase promoting complex/cyclosome (APC/C) leads to ubiquitination of securin, allowing cleavage of SCC1/RAD21 from centromeric cohesin complexes by separase and triggering the onset of anaphase [Uhlmann et al., 2000] (fig. 2).

### Shugoshins and Centromeric Cohesins

In somatic cells from higher organisms, most cohesin complexes from chromosome arms are released from chromatin during prophase and prometaphase by a mechanism that requires phosphorylation of the SA2/STAG2 cohesin subunit [Hauf et al., 2005]. During meiosis, arm cohesion is lost during the metaphase I/anaphase I transition by a process mediated by REC8 subunit cleavage from chromosome arms [Buonomo et al., 2000]. One relevant question is how centromeric cohesin complexes in mitosis are protected from phosphorylation until the metaphase/anaphase transition and how the centromeric cohesins are protected from separase cleavage until the second meiotic division. This problem was first resolved in fission yeast with the identification of a protein family called shugoshins (Japanese for 'guardian spirit'); Sgo1 and Sgo2 play a role in the centromeric protection of cohesin [Kitajima et al., 2004]. In fission yeast, Sgo1 is essential in meiosis, whereas Sgo2 is major in mitosis. Shugoshins protect centromeric cohesion in yeast mitosis and meiosis by recruitment of a specific subtype of serine/threonine protein phosphatase 2A, which blocks the cohesin phosphorylation necessary for removal of centromeric cohesion [Kitajima et al., 2006; Riedel et al., 2006] (fig. 3).

This review does not address the function of SGO proteins in meiosis in depth because there is a specific chapter about this field in this issue.



**Fig. 3.** Shugoshin and phosphatase PP2A protects centromeric cohesion. In fly and vertebrate mitosis, during the prophase-metaphase transition, the kinases Aurora B and/or Polo-like phosphorylate the SCC3 subunit of most cohesin complexes from chromosome arms and promote their dissociation from chromosomes. Shugoshin localizes at the centromeres and recruits the

phosphatase PP2A, which protects centromere cohesin complexes from phosphorylation. When all chromosomes are correctly bi-oriented at the metaphase plate, shugoshin and PP2A are delocalized from centromeres allowing the phosphorylation and separase degradation of centromere cohesins and the segregation of sister chromatids.

### Mitosis versus Meiosis

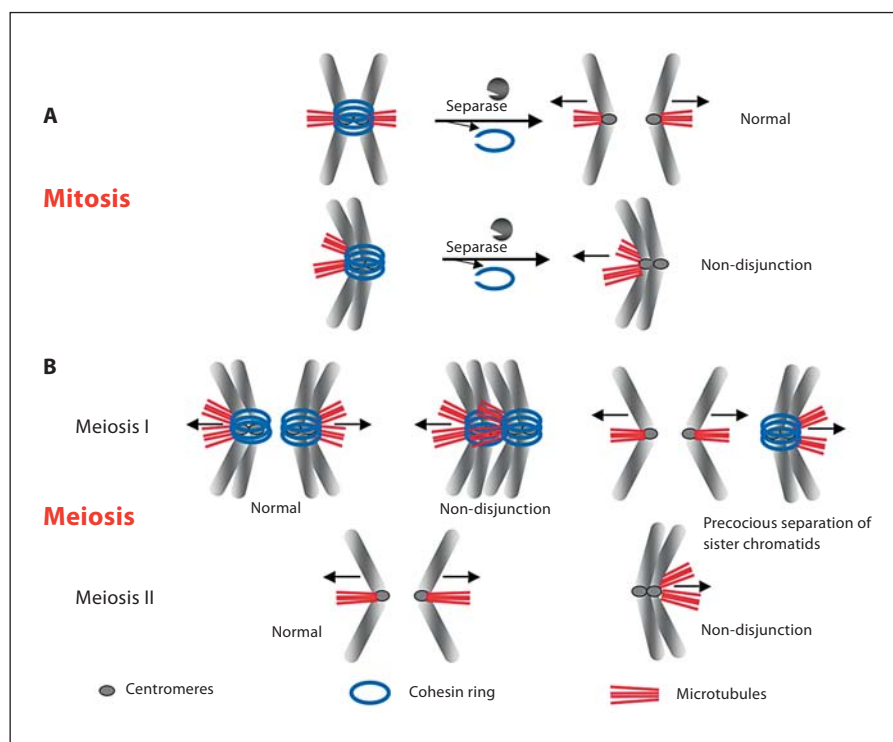
Meiosis presents 2 unique characteristics: (1) the formation and posterior destruction of a specific structure, the synaptonemal complex (SC), during prophase I, and (2) the participation of meiotic-specific cohesin subunits and different cohesin complexes on the control of chromosome arms and centromere cohesion during meiotic divisions. In mammals, only some of the protein molecules involved in the formation and control of SC are known. Three SC component proteins, SYCP1, SYCP2 and SYCP3, have been largely studied and new SC proteins, SYCE1, SYCE2 and TEX12, more recently characterized [for a review, see Suja and Barbero, 2009]. However, other proteins such as DIDO3 [Prieto et al., 2009] and HORMAD1 and HORMAD2 [Fukuda et al., 2010; Wojtasz et al., 2009] are emerging and appear to be important in the regulation of assembly and disassembly of SC. Anyway, a close spatio-temporal relationship between cohesin axes and axial elements of SC is needed for the successful pairing and synapsis of homologous chromosomes and for the correct meiosis progression (see the next section about animal models).

During meiosis I, the cohesin complexes at chromosome arms are removed during the metaphase I/anaphase I transition to allow segregation of recombined homologues to opposite poles (fig. 4). The centromeric cohesin complexes remain associated to chromosomes until the onset of anaphase II [Page et al., 2006; Revenkova and

Jessberger, 2006] (fig. 4). This is necessary to prevent premature separation of sister chromatids and aneuploidy in the resulting gametes.

STAG3, REC8, SMC1 $\beta$  meiosis-specific cohesins and RAD21 are also expressed in mammalian fetal oocytes, and their dynamics during early prophase I are similar to that in spermatocytes [Prieto et al., 2005]. Total loss of cohesin signals, as well as of SYCP2 and SYCP3, is nonetheless observed in both human and mouse oocytes as they progress through dictyate arrest [Kouznetsova et al., 2005; Prieto et al., 2005]; they are again detected on bivalents in metaphase I oocytes [Kouznetsova et al., 2005; Lee et al., 2006, 2008]. Studies of cohesion on *Smc1 $\beta$* -deficient oocytes [Hodges et al., 2005] and on oocytes from senescence-accelerated mice in which REC8, STAG3 and SMC1 $\beta$  were greatly reduced [Liu and Keefe, 2008] suggest that defective cohesin levels are associated with age-related non-disjunction in oocytes. More recently, in a study of the cohesin dynamic during meiosis in human oocytes, García-Cruz et al. [2010] showed that cohesins are present in human oocytes during meiotic arrest, although the REC8, STAG3 and SMC3 immunofluorescence signals were visualized as short filamentous structures instead of fully formed axes in this stage. All 4 subunits are observed at centromeres and along the chromosome arms, except at chiasmata during metaphase I, and are present at centromeric domains from anaphase I to metaphase II, suggesting a role for cohesins in sister chromatid cohesion during the 2 meiotic divisions in human oocytes.

**Fig. 4.** Sister chromatid cohesion and chromosome segregation during mitosis and meiosis. **A** During mitosis, sister chromatids are bi-oriented in metaphase and segregate correctly at anaphase (normal) or present synthetic orientation segregating the 2 sister chromatids to the same spindle pole (non-disjunction). **B** Normal meiosis I division results in the segregation of homologous chromosomes. Errors in the sister chromatid cohesion control could provoke that the homologues migrate together to the same pole (non-disjunction) or precocious separation of sister chromatids. During meiosis II, similar to mitosis, sister chromatid could segregate to a different pole (normal) or to the same pole (non-disjunction).



On the other hand, Lister et al. [2010], using a long-lived wild-type mouse strain, reported that cohesin levels decline gradually during the long prophase arrest that precedes MI in mouse oocytes. This cohesin loss may be amplified by an associated decline in the level of SGOL2 (mouse shugoshin 2 homolog), leading to chromosome missegregation during metaphase I and supporting a molecular link between cohesins/SGOL2 with female aging effect.

#### Mutant Mouse Models of Cohesins and/or Synaptonemal Complex Proteins

The characterization of mice deficient in either meiosis-specific cohesin subunits and/or in SC proteins has helped understand the biological role of these proteins during in vivo mammalian meiosis. The characterization of mouse *mei8*, a disrupted allele of *Rec8* induced by chemical mutagenesis, shows that homozygous mutant males and females are sterile and that REC8 is required to maintain chromosome synapsis, sister chromatid cohesion and chiasmata formation during prophase I [Bannister et al., 2004]. Another *Rec8* knockout model was generated by deletion of all coding exons of the mouse

*Rec8* allele by gene targeting [Xu et al., 2005]. The absence of REC8 function in these mice also provokes infertility in both sexes. These authors found that SC formation in mutant spermatocytes occurs between sister chromatids and not between homologue chromosomes, although they found no differences in SMC3 and RAD21 localization to that of wild-type in the earlier prophase I stages.

*Smc1 $\beta$*  mutant mice present complete male and female infertility, indicating an essential role of this cohesin for meiosis [Revenkova et al., 2004]. Male meiosis is blocked at pachytene, axial elements (AE) are shortened, homologue synapsis is incomplete, and chromosome arm and centromeric cohesion is lost prematurely. Although *Smc1 $\beta$* <sup>-/-</sup> oocytes also show problems in SC formation, they progress until metaphase II, but defective sister chromatid cohesion results in massive aneuploidy during meiotic divisions. A recent comparison of oocytes from *Sycp3*<sup>-/-</sup>, *Smc1 $\beta$* <sup>-/-</sup> and *Sycp3*<sup>-/-</sup>*Smc1 $\beta$* <sup>-/-</sup> double mutants suggested a distinct role for each SMC1 isoform ( $\alpha$  and  $\beta$ ) in meiotic AE/lateral elements (LE) organization [Novak et al., 2008].

An interesting model is the mouse deficient in *Sgol2*, a mammalian shugoshin orthologue essential for the completion of meiosis in mice. The loss of SGOL2 induces a precocious dissociation of the meiosis-specific REC8 cohesin complexes from anaphase I centromeres. Al-

though the meiosis progresses in mutant mice, this molecular alteration provokes the formation of aneuploid gametes and infertility [Llano et al., 2008].

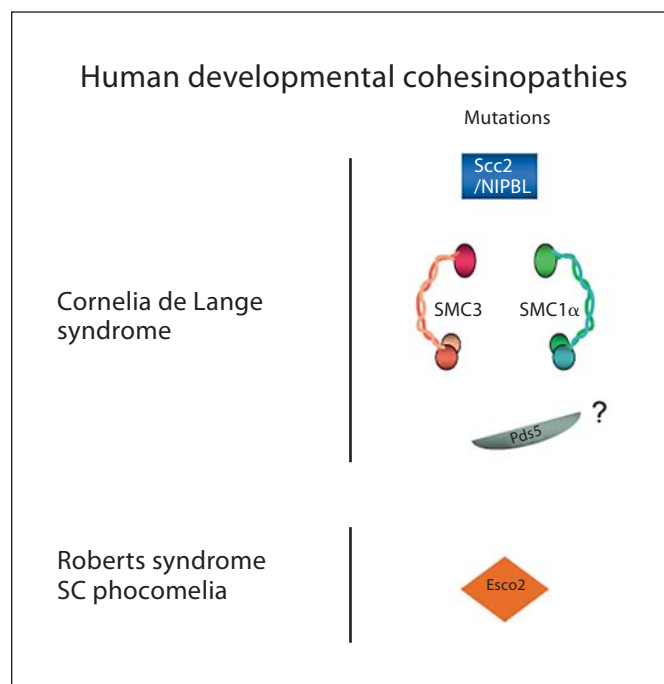
The absence of AE/LE proteins SYCP3 [Yuan et al., 2000] and SYCP2 [Yang et al., 2006] induces sexually dimorphic phenotypes; males are sterile due to a disruption in chromosome synapsis and a meiosis block in prophase I, whereas females are subfertile with reduced litter size and with embryo death due to an increase in aneuploid oocytes generated by chromosomal segregation errors. The checkpoints controlling homologue pairing and synapsis are, therefore, more restrictive in male germ cells [Kolas et al., 2005]. In contrast, the null mutants of transverse filaments/central element (TF/CE) proteins present distinct behavior relative to sexual dimorphism. Null mutation of *Sycp1* causes sterility in homozygous male and female mice. Most *Sycp1*<sup>-/-</sup> spermatocytes arrest at pachytene and show problems in repair/recombination and crossover formation [de Vries et al., 2005].

In addition to the initially characterized SYCP1 protein as the major component of CE of SC, 3 new components have been identified recently: SYCE1, SYCE2 and TEX12. These proteins interact together, and with SYCP1 during SC assembly, to form a correct CE [Costa et al., 2005; Hamer et al., 2006]. Meiosis is blocked at pachytene stage in *Syce1* null mutants, and the double-strand breaks (DSB) produced during prophase are not efficiently repaired in absence of SYCE1 [Bolcun-Filas et al., 2009]. The *Syce2* mutant mouse phenotype is very similar to that of *Sycp1* knockout mice. *Syce2*<sup>-/-</sup> mice can produce double-strand breaks and initiate recombination processes, but cannot complete SC formation; this results in male and female infertility [Bolcun-Filas et al., 2007]. The inactivation of the central element *Tex12* gene in mice results in: an incomplete homologous synapsis and incomplete maturation of early recombination events during prophase I [Hamer et al., 2008].

These phenotypes suggest inter-dependence among the distinct cohesin, AE and CE axes, and that absence of function of 1 component of these axes causes SC malformation, almost always provoking meiotic arrest at prophase I.

### Defective Control of Sister Chromatid Cohesion, Aneuploidy, Cancer and Other Cohesinopathies

As mentioned before, the correct control of sister chromatid cohesion is crucial for successful segregation of chromosomes. In addition to molecules implicated in the



**Fig. 5.** Cohesin and cohesin-regulators involved in the human developmental cohesinopathies. Mutations in the *SCC2/NIPBL* adherin gene are the cause of the most severe phenotype in Cornelia de Lange patients. Mutations in genes encoding for the cohesin subunits *SMC1α* and *SMC3* cause a mild variant of this syndrome. Although the phenotype of mice lacking the function of *PDS5A* and/or *PDS5B* exhibit developmental abnormalities such as Cornelia de Lange patients, currently there are no data found supporting mutations of these genes as a possible cause of this cohesinopathy in humans. A human orthologue of yeast, *Eco1* named *ESCO2*, is mutated in Roberts syndrome, which presents a very related phenotype as seen in Cornelia de Lange pathology.

spindle assembly checkpoint (SAC), which will be mentioned in another chapter of this issue, sister chromatid cohesion control proteins are involved in the correct amphitelic (or bi-orientation) of sister kinetochores in mitosis and meiosis II and in the unique chromosome behavior during meiosis I. This includes the maintenance of physical connections between homologues, posterior chiasmata resolution and the syntenic (mono-orientation) of sister kinetochores (fig. 4). Failures in centromeric proteins controlling correct bi-orientation or to establish a chiasma during meiosis I can result in the segregation of homologues to the same pole of MI spindle [Parra et al., 2004] (fig. 4). In addition, precocious separation of sister chromatids (PSSC) at meiosis I can cause the segregation of a whole chromosome and a single chromatid to the same pole (fig. 4). A typical error found during meio-

sis II is that sister chromatids are not separated (non-disjunction in meiosis II, fig. 4).

The loading of cohesin complex and the generation of cohesion are key processes in cell life. Mutations in gene encoding adherin *SCC2/NIPBL* are involved in the phenotype of human Cornelia de Lange Syndrome (CdLS) (OMIM 122470, 300590, 610759) [Krantz et al., 2004; Tonkin et al., 2004]. This pathology is a multiple neurodevelopmental disorder characterized by facial dysmorphisms, upper limb abnormalities, mental retardation, and growth delay. Later studies of several cases of this syndrome showed that mutations in *SMC1 $\alpha$*  and *SMC3* cause a mild variant of CdLS [Musio et al., 2006; Dear-dorff et al., 2007] (fig. 5).

Mutations in the gene encoding for human *ESCO2*, a homolog to yeast *Eco1* acetyltransferase, were found responsible for the human Roberts syndrome/phocomelia (RBS) (OMIM 268300) [Vega et al., 2005] (fig. 5). This is an autosomal recessive disorder related phenotypically to CdLS; patients present craniofacial abnormalities, limb reduction and growth retardation. Cells from RBS patients show lack of cohesion at the heterochromatic regions around centromeres and at the Y chromosome long arm [Van Den Berg and Francke, 1993].

Mice that lack *PDS5B* die shortly after birth and have multiple developmental anomalies that resemble those found in humans with CdLS [Zhang et al., 2007]. The study of chromosomes from *Pds5B*<sup>-/-</sup> mouse cells showed no defects in sister chromatid cohesion. In addition, *Pds5A* deficiency results in developmental abnormalities similar to those present in *Pds5B* knockout mice [Zhang et al., 2009]. However, a recent study looking for mutations in *PDS5A* gene in 137 Italian CdLS patients, who do not have mutations in *Scs2/NIPBL*, *SMC1 $\alpha$*  nor *SMC3*, was negative [Oliver et al., 2010]. These 2 syndromes have been recently described as cohesinopathies, and they were excellently reviewed in Liu and Krantz [2008].

Mutations in the *RECQL4* gene encoding for a human RecQ DNA helicase are found in a large fraction of type II Rothmund-Thomson syndrome (OMIM 268400) patients. This is a rare autosomal recessive genetic disorder characterized by a congenital skin rash, skeleton birth defects, genomic instability, and cancer predisposition. Mann et al. [2005] generated a viable *Recql4* mutant mouse and found that the cells have high frequencies of premature centromere separation and aneuploidy, suggesting a new role for *RECQL4* in sister chromatid cohesion. On the other hand, overexpression of separase, the endopeptidase that cleaves *SCC1* cohesin subunit and

triggers anaphase, induces premature separation of sister chromatids, lagging chromosomes and anaphase bridges in an in vivo mouse mammary transplant model [Zhang N et al., 2008a]. Separase is found to be significantly over-expressed in human breast tumors, suggesting that over-expression of separase induces aneuploidy and tumorigenesis.

Recently, different somatic mutations were characterized in more than 130 cases of colorectal cancer. Six mutations map to 3 cohesin subunit genes, *SMC1 $\alpha$* , *SMC3* and *STAG3* and 4 to a cohesin cofactor *SCC2/NIPBL* gene [Barber et al., 2008]. Colorectal cancer cells are characterized by chromosomal instability and high rates of chromosome missegregation; these problems could be due to an aberrant cohesin dynamic resulting from cohesin mutations [reviewed in Mannini et al., 2010]. All these results strongly support that cohesin plays an essential role in genome stability and chromosome aneuploidy.

### Concluding Remarks

Aneuploidy is a characteristic feature of human malignancies and has been proposed as a frequent event in tumor formation and progression [Kops et al., 2005]; however, the molecular mechanisms yielding aneuploidy remain an essential, unresolved problem in cancer biology. Malfunction of molecules involved in chromosome segregation during mitosis and meiosis frequently results in aneuploidy. Cohesins emerged just over a decade as key protagonists in chromosome segregation during cell division, regulating sister chromatid cohesion. During this period, a lot of effort has been developed to elucidate the structure and role of cohesin complex and on the characterization of the cohesin-interacting proteins that modulate cohesin complex function. All these findings, which have been summarized in this review, locate cohesins and cohesin-regulators as essential players in the molecular mechanisms that generate aneuploidies, resulting in human pathologies such as Down syndrome, tumor formation and progression, and infertility. In addition, in the last 5 years, 2 different approaches based on the generation of mice deficient in cohesin function, on one hand, and the identification and characterization of mutations of cohesin and cohesin-regulator genes in human syndromes, on the other hand, have revealed new and important roles for cohesins in gene expression control and in chromosome stability, improving our understanding of chromosome dynamics during cell division. However, there are still many unanswered questions concerning



the different molecules involved and the differences in the control of sister chromatid cohesion between mitosis and meiosis. The future research on structure and role of molecular partners of cohesins that modulate the function of cohesin complex during cell division is an exciting and crucial task in our aspiration to learn more about the molecular bases of aneuploidy.

## Acknowledgements

I apologize to all colleagues whose contributions have not been referenced due to space restrictions. This work was supported by the Spanish Ministerio de Ciencia e Innovación (grant BFU2009-08975/BMC) and the Comunidad de Madrid (grant P-BIO-0189-2006).

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