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Sister chromatid cohesion and recombination in meiosis

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Abstract. Sister chromatids are associated from their formation until their disjunction. Cohesion between sister chromatids is provided by protein complexes, of which some components are conserved across the kingdoms and between the mitotic and meiotic cell cycles. Sister chromatid cohesion is intimately linked to other aspects of chromosome behaviour and metabolism, in particular chromosome condensation, recombination and segregation. Recombination, sister chromatid cohesion and the relation between the two processes must be regulated differently in mitosis and meiosis. In meiosis, cohesion and recombination are modified in such a way that reciprocal exchange and reductional segregation of homologous chromosomes are ensured.

Mitosis

The mechanism of sister chromatid cohesion has been analysed in most detail in mitosis. We will therefore summarise the roles of sister chromatid cohesion in the mitotic cycle before we turn to meiosis.

Mitotic sister chromatid cohesion and chromosome disjunction

Sister chromatid cohesion is essential for the faithful segregation of chromosomes during mitosis. In the mitotic cycle, sister chromatids are associated from S-phase until anaphase along their arms and in their centromeric regions (Selig et al. 1992; Guacci et al. 1994). In higher eukaryotes, cohesion is most persistent in heterochromatic domains containing large blocks of repetitive DNA (Lica et al. 1986; Cooke et al. 1987; Sumner 1991; Carmena et al. 1993; Warburton and Cooke 1997). Possible sources of cohesion that have been proposed are: DNA catenations that persist from replication (Murray and Szostak 1985), proteins that glue sister chromatids together, or a combination of these factors. Whereas catenation is dispensable for cohesion, at least in yeast (Koshland and Hartwell 1987), several proteins have been identified during the last few years that are essential for mitotic sister chromatid cohesion and/or its regulation. Most of these proteins are conserved among eukaryotes, and have been analysed in detail in budding yeast (*Saccharomyces cerevisiae*) (Table 1). In yeast, at least four proteins contribute stoichiometrically to a multi-subunit complex, called cohesin, which is essential for sister chromatid cohesion: Mcd1/Scc1, Scc3, Smc1 and Smc3 (Guacci et al. 1997; Michaelis et al. 1997; Toth et al. 1999). The cohesin complex binds to chromosomes from late G1 onwards (Toth et al. 1999), and cohesin-mediated links between sister chromatids are established after passage of the replication forks, with the catalytic help of Eco1/Ctf7 (Skibbens et al. 1999; Toth et al. 1999; Uhlmann et al. 1999). The cohesin complex probably binds to chromosomes by direct interaction with specific DNA sequences. Smc1 and Smc3 belong to an ancient family of modulators of chromosome structure; they form heterodimers and are capable of binding to chromatids, possibly

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Table 1. Budding yeast proteins with a role in mitotic sister chromatid cohesion are conserved among eukaryotes

Protein (*S. cerevisiae*)	Role in cohesion	Homologous proteins (species)	References
Mcd1/Scc1	Cohesin		Guacci et al. (1997); Michaelis et al. (1997)
		Rad21 (*S. pombe*)	Birkenbihl and Subramani (1992)
		hHR21 (*Homo sapiens*)	McKay et al. (1996)
		XRAD21 (*Xenopus laevis*)	Losada et al. (1998)
		PW29 (*Mus musculus*)	Darwiche et al. (1999)
Scc3/Irr1	Cohesin		Toth et al. (1999)
		Rec11 (*S. pombe*)	de Veaux and Smith (1994)
Smc1	Cohesin		Michaelis et al. (1997)
		bSMC1 (*Bos bovis*)	Stursberg et al. (1999)
		XSMC1 (*X. laevis*)	Losada et al. (1998)
		hSMC1 (*H. sapiens*)	Schmiesing et al. (1998)
		mSMCB (*M. musculus*)	Darwiche et al. (1999)
Smc3	Cohesin		Michaelis et al. (1997)
		SUDA (*A. nidulans*)	Holt and May (1996)
		DCAP (*D. melanogaster*)	Hong and Ganetzky (1996)
		bSMC3 (*B. bovis*)	Stursberg et al. (1999)
		XSMC3 (*X. laevis*)	Losada et al. (1998)
		hSMC3 (*H. sapiens*)	Schmiesing et al. (1998)
		mSMCD (*M. musculus*)	Darwiche et al. (1999)
Scc2	Adherin		Michaelis et al. (1997); Toth et al. (1999)
		Mis4 (*S. pombe*)	Furuya et al. (1998)
		Rad9 (*C. cinereus*)	Seitz et al. (1996)
		Nipped-B (*D. melanogaster*)	Rollins et al. (1999)
Eco1/Ctf7	Establishment	–	Toth et al. (1999); Skibbens et al. (1999)
Pds1	Securin		Yamamoto et al. (1996);
		PTTG (*X. laevis)*: functional homologue?	Cohen-Fix et al. (1996; Ciosk et al. (1998) Funabiki et al. (1996)
		Cut2 (*S. pombe*): functional homologue?	Zou et al. (1999)
Esp1	Separin		Ciosk et al. (1998; Uhlmann et al. (1999)
		BIMB (*A. nidulans*)	May et al (1992)
		Cut1 (*S. pombe*): functional homologue?	Funabiki et al. (1996)

through transient interaction with the adherin Scc2 (Toth et al. 1999). In vitro, Smc1 binds to DNA, in particular to double-strand DNA with AT-rich sequences and to sequences with a tendency to form secondary structures (Akhmedov et al. 1998). In yeast, Smc1 and Mcd1/Scc1 bind predominantly to AT-rich regions (Blat and Kleckner 1999; Tanaka et al. 1999). In yeast centromeres, a highly specialised chromatin structure is required for binding of Mcd1/Scc1 (Tanaka et al. 1999). Proteins that determine chromatin conformation may thus influence cohesion. Mcd1/Scc1 and Scc3 possibly provide intermolecular links between Smc3/Smc1 heterodimers that are bound to different sister chromatids (Toth et al. 1999). In short, as we will discuss in more detail below, most available evidence suggests that cohesins physically connect sister chromatids, but direct evidence for this is lacking.

Dissolution of sister chromatid cohesion depends on the anaphase-promoting complex APC, which ligates ubiquitin to proteins and thus targets them for proteolysis (Irniger et al. 1995). APC can associate with so-called activator proteins, which specify which protein(s) will be ubiquinated, and when. In the mitotic cycle, Pds1 becomes an APC target (Cohen-Fix et al. 1996) upon association of the activator protein Cdc20 with APC (Visintin et al. 1997). Pds1 inhibits anaphase by capturing the separin protein Esp1 (Ciosk et al. 1998). Upon liberation from Pds1, Esp1 promotes cleavage of Mcd1/Scc1 (Uhlmann et al. 1999). This probably destabilises the cohesin complex, so that Mcd1/Scc1 and Scc3 dissociate from the chromatin (Michaelis et al. 1997; Toth et al. 1999). Cohesin, in particular Mcd1/Scc1, is thus a target for the regulation of cohesion, but it is possible that other proteins are responsible for the mechanical strength of cohesion.

In yeast, dissociation of Mcd1/Scc1 from the chromatin coincides with the actual separation of sister chromatids at the onset of anaphase (Michaelis et al. 1997; Toth et al. 1999). Before chromatid disjunction, between S-phase and G2/M, the ratio of Mcd1/Scc1 and Smc1 in centromeres to Mcd1/Scc1 and Smc1 in the arms increases (Blat and Kleckner 1999). The relative amount of cohesin in centromeric regions possibly increases during G2/M-phase because higher order chromosome condensation causes some loss of cohesin from the arms, although it cannot be excluded formally that centromeres bind more cohesin during G2/M. Even so, minimal yeast centromeres by themselves cannot withstand the forces exerted by the spindle microtubules; they also need some flanking (arm) cohesion for this (Tanaka et al.

1999). Although cohesin is more abundant in centromeric regions than in the arms of yeast G2/M chromosomes, there are no indications that release of arm and centromeric cohesion is differentially regulated. In yeast cells arrested in G2/M-phase by a microtubule-depolymerising agent (nocodazole), sister chromatids remain associated along their arms and centromeres (Guacci et al. 1994).

In higher eukaryotes, differentiation of cohesion along mitotic metaphase chromosomes is more pronounced than in yeast. In contrast to yeast chromosomes eukaryotik, chromosome visibly lose arm cohesion before centromeric cohesion during mitosis in some animal cells (Sumner 1991). Moreover, mammalian cells arrested in metaphase by a microtubule-depolymerising agent (colchicine) separate sister chromatid arms but maintain centromeric cohesion (reviewed in Rieder and Cole 1999). Such a differentiation in cohesion along the chromosome might be mediated by local differences in the affinity or concentration of residual cohesin-binding sites, and/or through association of specific proteins (reviewed in Miyazaki and Orr-Weaver 1994; Tanaka et al. 1999). In *Drosophila*, the Mei-S332 protein localises to the centromeres during prometaphase before microtubules attach to the kinetochores (Tang et al. 1998) and dissociates from the centromeres at anaphase when sister chromatids disjoin (Moore et al. 1998). Mei-S332 thus possibly contributes to maintenance of centromeric cohesion when chromosomes align on the metaphase plate (congression).

It is uncertain whether cohesins fulfil similar roles in mitotic chromosome segregation of higher eukaryotes (reviewed by Nasmyth 1999). In *Xenopus* extracts, most cohesin dissociates already from the chromosomes in mitotic prometaphase (Losada et al. 1998). Possibly, a small fraction of cohesin links persists and contributes to proper chromosome segregation in animal cells, or cohesin complexes have no role in chromosome segregation in animal mitosis but function only in G2, for instance in DNA repair. Other factors would then maintain cohesion until anaphase in higher eukaryotes. Catenation and association of heterochromatic domains have been considered as such factors. Sister chromatids are catenated after DNA replication, and require topoisomerase II for separation (reviewed by Holm 1995), in particular of the arms, and not of the centromeres (Funabiki et al. 1993; reviewed by Rieder and Cole 1999). However, there is no positive evidence that catenation is required for maintenance of cohesion in higher eukaryotes. Association of heterochromatic domains contributes to cohesion of sister chromatids throughout their length but in particular to centromeric cohesion (reviewed by Allshire 1997). However, it is possible that such associations are due to the ability of heterochromatin of the appropriate conformation to bind Mcd1/Scc1 (Tanaka et al. 1999).

In many higher eukaryotes mitotic centromeric and arm cohesion are differentially regulated (Bardhan 1997; Rieder and Cole 1999). In *Drosophila*, at least two genes, *pim* (*pimples*) and *thr* (*three rows*), are specifically required for release of centromeric cohesion (Stratmann and Lehner 1996). Furthermore, sister chromatid separation depends on the presence of tension on all kinetochores (Nicklas et al. 1995). Bipolar tension leads to loss of some phosphoepitope(s) from kinetochores in mammalian cells (Gorbsky and Ricketts 1993). These epitope(s) are not found on chromatid arms; they probably emit a signal that prevents release of centromeric cohesion (Campbell and Gorbsky 1995).

Mitotic sister chromatid cohesion and recombinational repair

While centromeric cohesion primarily serves disjunction, arm cohesion plays additional roles in recombinational repair. Various mutants with defects in sister chromatid cohesion are also radiation sensitive and/or defective in DNA double-strand break (DSB) repair (Table 2). Furthermore, two cohesin components, Smc1 and Smc3, are part of the recombinational repair complex RC1 (Jessberger et al. 1996; Stursberg et al. 1999), and Smc1/3 heterodimers promote re-annealing of complementary DNA strands (Jessberger et al. 1996).

Sister chromatid cohesion and recombination are linked in various ways: at the level of cell cycle regulation, overall chromosome organisation and individual protein complexes or proteins (Table 2).

Cohesins provide links between recombination and cohesion at all these levels (reviewed in Strunnikov and Jessberger 1999). At the chromosomal level, they provide the proximity of an undamaged template for recombinational repair and possibly enable communication between sister chromatids: if one chromatid is damaged, the sister has to be prepared for repair. The presence of common components in cohesin and recombination complexes furthermore indicates that sister chromatid cohesion and recombinational repair make use of similar mechanisms. For example, stabilisation of recombination intermediates might require a mechanism resembling that used for sister chromatid cohesion. Some non-cohesin proteins involved in recombinational repair, including Rad50, share structural features with Smc proteins (reviewed in Jessberger et al. 1998; Strunnikov and Jessberger 1999) and possibly recognise similar DNA structures and/or fulfil similar steps.

Individual cohesin complexes may furthermore function as nucleation sites for the assembly of DNA repair complexes, and this in turn may have resulted in a sisterbiased recombinational repair pathway. The Rad50/Xrs2/Mre11 complex in yeast (see Fig. 1) has a role in various mitotic DSB repair pathways, including recombinational repair (reviewed in Pâques and Haber 1999). *rad50* mutants of budding yeast are radiation sensitive and hyperrec (Malone and Hoekstra 1984; Malone et al. 1990): they display more interchromosomal mitotic recombination than wild type. Possibly, certain DNA damage cannot be repaired on the sister chromatid in these mutants and is therefore channelled into interchromosomal repair pathways (Pâques and Haber 1999). Interestingly, mutants of *RAD21* (the *MCD1/SCC1*-homologous gene of fission yeast) are also hyperrec (Grossenbacher-Grunder and Thuriaux

Table 2. Links between cohesion and recombinational repair in mitosis

Protein (species)	Link with cohesion	Link with recombinational repair	References
Pds1 (*S. cerevisiae*)	Separin	*pds1-1* mutant: no inhibition of cell cycle progression in response to DNA damage; γ-radiation sensitive	Yamamoto et al. (1996)
Mcd1/Scc1 (*S. cerevisiae*)	Cohesin component	*mcd1-1* mutant: radiation sensitive	Guacci et al. (1997)
Rad21 (*S. pombe*)	Homologous to Mcd1/Scc1	*rad21–45* mutant: γ-radiation sensitive, defective in DSB repair; *rad21-45* mutant: hyperrec	Birkenbihl and Subramani (1992) Grossenbacher-Grunder and Thuriaux (1981)
bSMC1 and bSMC3 (*B. bovis*)	Homologous Smc1 and Smc3	Hetero-dimer promotes re-annealing of complementary DNA strands in vitro; components of recombinational repair complex RC1	Jessberger et al. (1996) Stursberg et al. (1999)
Rad9 (*C. cinereus*)	Homologous to Scc2	*rad9-1* mutant: γ-radiation sensitive; *Rad9* mRNA: induced after γ-radiation	Zolan et al. (1988) Seitz et al. (1996)
Spo76[a] (*S. macrospora*)	*spo76-1* mutant: transient cohesion defect at prometaphase	*spo76-1* mutant: UV- and X-ray sensitive	van Heemst et al. (1999) Moreau et al. (1985; Huynh et al. (1986)
BimD[a] (*A. nidulans*)	*bimD5*, *bimD6* mutants: blocked at metaphase/anaphase; *sudA* (homologous to *Smc3*): suppressor of segregation defect of *bimD6*	*bimD5*, *bimD6* mutants: UV and MMS sensitive	Denison et al. (1993) Holt and May (1996)

[a] Spo76 and BimD are homologous proteins

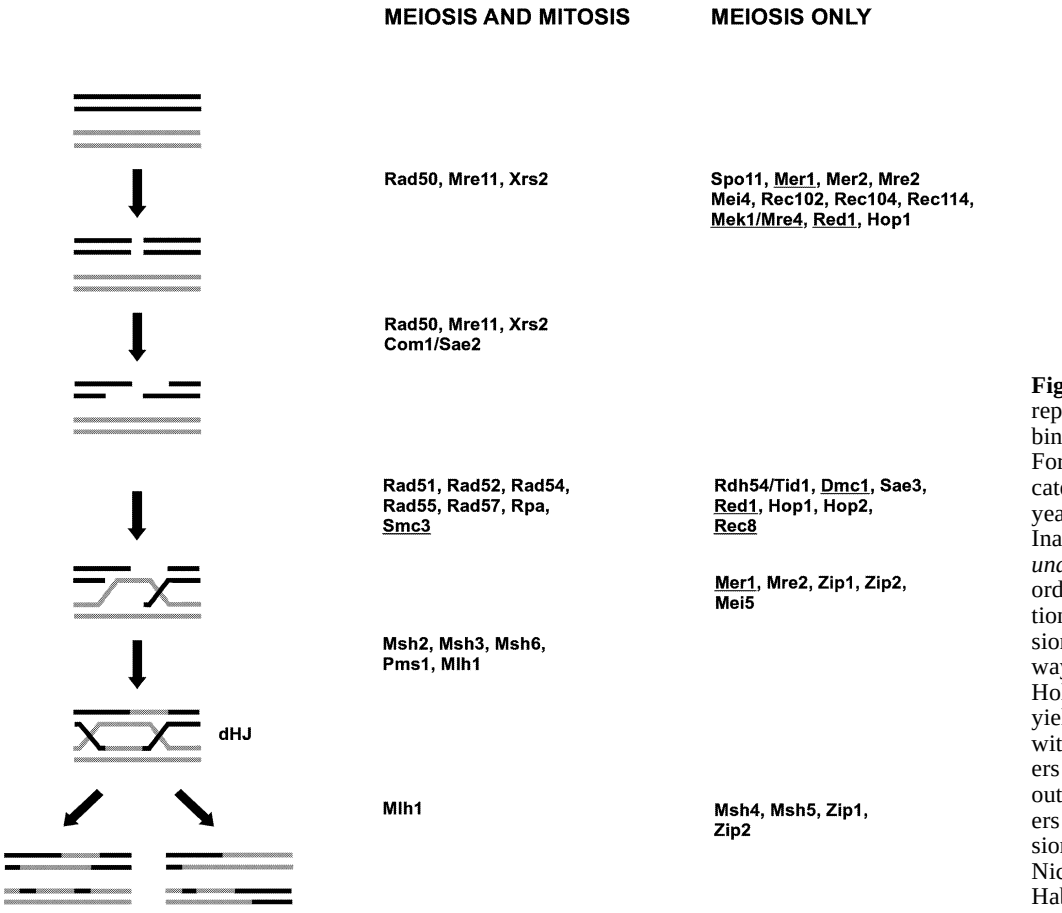

Fig. 1. The double-strand break repair model of meiotic recombination (Szostak et al. 1983). For each step it has been indicated which proteins of budding yeast are most likely involved. Inactivation of each of the *underlined* proteins causes coordinated defects in recombination and sister chromatid cohesion. In the last step of this pathway, resolution of the double Holliday junction (*dHJ*) can yield recombinant molecules with exchange of flanking markers (crossover) (*right*) or without exchange of flanking markers (*left*). For details and discussion, see reviews by Smith and Nicolas (1998) and Pâques and Haber (1999)

1981). Possibly, Mcd1/Scc1 (Rad21) contributes to the preference for the sister chromatid as template in Rad50-mediated recombinational repair.

Spo76/BimD provides an example of a link between recombination and cohesion at the level of chromosome organisation (Table 2). The *Sordaria* Spo76 protein is chromosome associated, except in mitotic and meiotic metaphase and anaphase (van Heemst et al. 1999). In mitotic prometaphase, the non-null allele *spo76-1* causes regional, co-ordinate defects in chromosome condensation and sister chromatid cohesion (van Heemst et al. 1999). In *Aspergillus nidulans* two non-null alleles, *bimD5* and *bimD6*, cause a block at the mitotic metaphase/anaphase transition (Denison et al. 1993). These results suggests that Spo76/BimD influence the strength of cohesion. Because *SUDA* (orthologous to *SMC3*) carries an extragenic suppressor mutation for *bimD6* (Holt and May 1996), Spo76/BimD probably influences cohesion through interaction with cohesin. Importantly, the defects in cohesion and chromosome organisation are accompanied by radiation sensitivity (Table 2). Because cohesion is important for recombinational DNA repair (see above), radiation sensitivity could be a straightforward effect of defective cohesion. It is also possible that repair of radiation-induced DNA damage causes local alterations in chromatin conformation that put cohesion to the test and aggravate the cohesion defect in these mutants. Chromosome condensation might also put a strain on cohesion and result in local loss of cohesion in mitotic prometaphase of *spo76-1* mutants.

Cohesion and recombination are also linked through the cell cycle. The cell monitors DNA damage and progression of recombination and repair and relates it to cell cycle progression, whereas cohesin is an important target for the cell cycle regulatory machinery (reviewed by Nasmyth 1996, 1999). Pds1 is not only important for inhibiting the release of cohesion until the metaphase/anaphase transition but is also directly involved in the mitotic G2 DNA damage cell cycle checkpoint. The temperature-sensitive *pds1-1* mutant of budding yeast (Table 2) is unable to inhibit anaphase and other aspects of cell cycle progression (cytokinesis, DNA replication and bud formation) in response to DNA damage. *pds1-1* mutants are therefore γ-irradiation sensitive (Yamamoto et al. 1996).

The link between cohesion and recombination manifests itself by the preference of all analysed eukaryotes for the sister chromatid above the homologous chromosome as template for mitotic DSB repair (Latt 1981; Kadyk and Hartwell 1993; Richardson et al. 1998). In yeast, the major recombination repair pathway in diploid G2 utilises the sister chromatid and requires Rad54 (Arbel et al. 1999), whereas a minor pathway is homologue oriented and depends on Rad54 and/or a paralogous protein, Tid1/Rhd54 (Klein 1997; Arbel et al. 1999).

A bias for the sister chromatid in recombinational repair prevents various problems for the mitotic cell. It precludes ectopic recombination, and obviates segregation problems. Interhomologue crossovers will give rise to a bivalent configuration (compare Fig. 2A), which will probably hamper the sister kinetochores of the crossover chromosomes in capturing microtubules from opposite poles of the spindle (Chua and Jinks-Robertson 1991). A bias for the sister chromatid will furthermore prevent loss of heterozygosity distal to the crossover. Loss of heterozygosity is a problem if homologous chromosomes are not entirely equivalent because of heterozygosity or genomic imprinting (Moulton et al. 1996). These disadvantages of mitotic crossing over probably not only favoured the development of an intersister bias in mitotic recombinational repair but also enhanced the development of specialised mechanisms for dealing with the interhomologue interactions that nevertheless occur. In mammalian cells, almost all interhomologue interactions result in gene conversions rather than crossovers (Richardson et al. 1998), possibly because repair mechanisms predominate that primarily yield conversions, such as synthesis-dependent strand annealing (SDSA; reviewed in Pâques and Haber 1999). In yeast, the *RAD9* gene prevents homology-directed reciprocal translocations (Fasullo et al. 1998), presumably by activating enzymes of the non-homologous end-joining pathway (Mills et al. 1999). If, despite these precautions, mitotic crossovers are formed, the weakness of mitotic arm cohesion or the release of arm cohesion before centromeric cohesion may facilitate the resolution of mitotic bivalents at the mitotic metaphase/anaphase transition.

To summarise, the role of cohesins in recombinational repair is conserved throughout eukaryotes and includes the direction of recombinational repair towards the sister chromatid in mitotically dividing cells.

Meiosis

Meiotic recombination and chromosome behaviour

Meiosis is responsible for two essential features of the sexual life cycle: the transition from the diploid to the haploid state and the generation of new combinations of alleles.

Meiosis has probably evolved from a mitosis-like process by adaptation of the cell cycle and chromosome behaviour (see discussion in Kleckner 1996). In the mitotic cycle, one round of DNA replication is followed by one nuclear division, whereas in meiosis, a single S-phase is followed by two successive nuclear divisions, meiosis I and II. Most differences between chromosome behaviour in mitosis and meiosis I concern recombination and the relation between sister chromatids. Recombination occurs at a 100-to 1000-fold higher frequency in meiosis than in mitosis. The meiotic prophase cell actively initiates recombination, and it does so preferentially at certain chromosomal loci called hotspots. In meiosis, recombination is directed preferentially towards the homologous chromosome rather than the sister chromatid. A large proportion of meiotic recombination events are resolved as crossovers, at least in yeast. The distribution of crossovers along the chromosomes is controlled in such a way that there is at least one crossover (obligate crossover) per pair of homologues (biva-

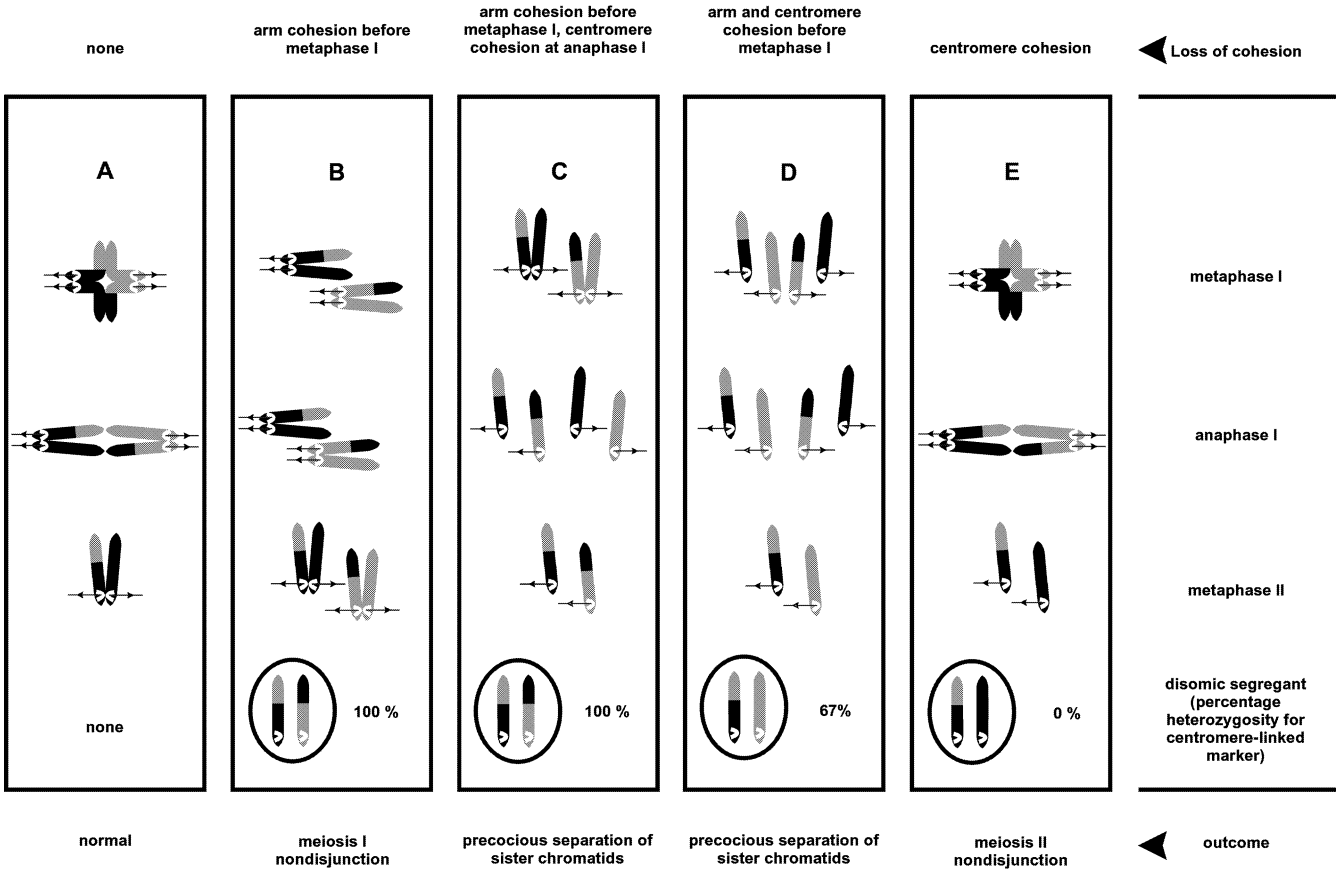

Fig. 2A–E. Loss of arm cohesion and/or centromere cohesion and the effects on chromosome disjunction and segregation of centromere-linked markers in meiosis. At the *top* of the figure is indicated where and when cohesion is lost. Panel **A** shows chromosome segregation if cohesion is normal. Panels **B–E** show aberrant segregation patterns resulting from various types of cohesion loss. Each of these panels shows only one of the possible segregation patterns that result from loss of cohesion and will yield a disomic ascospore. Kinetochores are indicated as *white, cup-shaped entities*, and non-sister chromatids are differently *shaded*. The *ovals* at the bottom of panels **B–E** represent disomic ascospores that can arise from aberrant segregation; beside these ovals is indicated the percentage of all disomic ascospores that will be heterozygous for a centromere-linked marker. **A** If cohesion is normal, recombined homologous chromosomes disjoin at meiosis I and sister chromatids at meiosis II to form haploid segregants. **B** If arm cohesion, but not centromeric cohesion, is lost before metaphase I, homologous chromosomes can nondisjoin at meiosis I, whereas chromatids will separate normally (equationally) at meiosis II; this can lead to disomic ascospores, of which 100% will be heterozygous for centromere-linked markers of the nondisjoined chromosome. Panels **C–E** show chromosome segregation patterns resulting from other types of cohesion loss. The four types of aberrant chromosome segregation that can occur are: **B** meiosis I nondisjunction of homologous chromosomes; **C**, **D** precocious separation of sister chromatids; panel **C** shows precocious separation of sister chromatids at meiosis I, with equational sister segregation, and panel **D** shows random segregation of sister chromatids at meiosis I. Note that disomics resulting from meiosis I segregation errors (panels **B–D**) are predominantly heterozygous for centromere-linked markers, whereas disomics resulting from meiosis II nondisjunction (panel **E**) are 100% homozygous for centromere-linked markers

lent); if multiple crossovers occur, they are maximally spaced (crossover interference). Finally, most meiotic recombination events occur in the context of a prominent proteinaceous structure, the synaptonemal complex (SC) (reviewed by Heyting 1996). Synaptonemal complexes are assembled between homologous chromosomes during meiotic prophase. First, a single axial element (AE), which is shared by the two sister chromatids, is assembled along each chromosome; subsequently, the AEs of homologous chromosomes are connected by numerous transverse filaments to form the structure of an SC. As is discussed in more detail below, SCs (or components thereof) have a role in steering meiotic recombination in the right direction (the homologous chromosome) and in regulating the number and distribution of crossovers along the bivalents.

Most species form on average about two crossovers per bivalent. The crossovers serve a dual role: they yield new combinations of alleles, and they have a mechanical role in the most specific feature of meiotic chromosome behaviour: the disjunction of homologous chromosomes at meiosis I.

Meiotic sister chromatid cohesion and chromosome disjunction

Disjunction of homologous chromosomes in meiotic anaphase I requires that bivalents rather than individual chro-

mosomes line up on the metaphase I spindle (Fig. 2A; reviewed in Moore and Orr-Weaver 1998). The two sister kinetochores of a meiotic metaphase I chromosome do not separate, as in mitosis, but they act as a single unit and retain the same orientation, so that they attract microtubules from only one pole of the metaphase I spindle. The bivalent orients itself because the still united sister kinetochores of the homologous chromosome catch microtubules from the opposite pole. The crossover(s) and the cohesion between sister chromatid arms distal to the crossover(s) (reviewed by Maguire 1990) prevent a bivalent falling apart when it experiences the opposite poleward pulling forces of the microtubules during congression (Fig. 2A). At anaphase I, arm cohesion is released, so that homologous chromosomes disjoin (reductional division). Centromeric cohesion is maintained until anaphase II. Between anaphase I and metaphase II, the orientation of the sister kinetochores changes so that they can catch microtubules from opposite poles of the metaphase II spindle. Finally, at anaphase II, cohesion at the centromeres is lost so that sister chromatids segregate (equational division).

Thus, as in mitosis of higher eukaryotes, in meiosis sister chromatid cohesion is released in two steps. However, in meiosis, loss of cohesion is spread over two divisions: arm cohesion distal to crossovers is released in meiosis I and centromeric cohesion in meiosis II. Furthermore, sister kinetochores retain the same orientation and act as a single unit at meiosis I, and lose co-orientation between anaphase I and metaphase II (Suja et al. 1999). In budding yeast, the *SPO13* gene plays a pivotal role in these meiotic adaptations of chromosome behaviour through modification of the cell cycle (see below).

Meiotic recombination

Meiotic recombination is initiated by double-strand DNA scission, and probably proceeds largely according to the DSB repair model (Fig. 1) of Szostak et al. (1983) (reviewed by Smith and Nicolas 1998; Pâques and Haber 1999).

The endonuclease that makes meiotic DSBs is almost certainly Spo11, a topoisomerase II-like enzyme, which is thought to cleave double-stranded DNA by a transesterification reaction (Bergerat et al. 1997; Keeney et al. 1997) and remains covalently attached to the 5′ ends of the break (de Massy et al. 1995; Keeney and Kleckner 1995; Liu et al. 1995). Several additional proteins,which probably create the right preconditions and context for meiotic DSB, are involved in this step.

Spo11 is subsequently removed, and the 5′ ends are resected. According to the model of Szostak et al. (1983), one of the resulting 3′ tails (Fig. 1) then invades a homologous region of a donor DNA duplex, displacing a small D-loop. This D-loop would then be enlarged by repair synthesis primed from the invading 3′ end; the enlarged D-loop would eventually contain sequences complementary to the 3′ end from the other side of the gap, and anneal. A second round of repair synthesis would then follow from this 3′ end (Szostak et al. 1983). Some or all DSBs are ultimately converted to a form of joint molecule (JM) that consists of two DNA duplexes connected by a double-Holliday junction (Fig. 1, dHJ). In suitable experiments, JMs between sister chromatids (intersister JMs) can be distinguished from interhomologue JMs. The preference for the homologous chromosome above the sister chromatid could therefore be demonstrated at this step in meiotic recombination (Schwacha and Kleckner 1994, 1997): in wild-type yeast meiosis, the intersister JMs are several-fold more frequent than interhomologue JMs (Schwacha and Kleckner 1997). The JMs are finally resolved into mature recombinant DNA molecules.

Some observations on meiotic recombination are not easily explained by the Szostak model; for the later steps in meiotic recombination alternative mechanisms have been considered in detail, in particular SDSA (see review by Pâques and Haber 1999 and references therein).

Meiotic sister chromatid cohesion and recombination

Most genes involved in mitotic recombinational repair of DSBs are also required for meiotic recombination (Fig. 1). However, recombinational repair of DSBs is heavily modified and adapted in meiosis, as is evident from the requirement of meiosis-specific genes for many steps in the recombination process (Fig. 1). These adaptations include an altered relationship between recombination and sister chromatid cohesion. We have argued that in mitosis cohesin complexes are involved in both cohesion and sister chromatid-based recombinational repair. In meiosis, recombination has to be directed towards the homologue but, at the same time, arm cohesion has to be maintained and possibly even reinforced to ensure correct reductional segregation of chromosomes at meiosis I (Fig. 2A). One possible solution to this problem would have been to unlink meiotic recombination from sister chromatid cohesion, but this has not happened: several genes have a role in both meiotic recombination and sister chromatid cohesion (Table 3), including genes involved in mitotic cohesion and DNA repair (compare Tables 1, 2 and 3).

Recently, it has turned out that not only the recombination machinery but also the cohesin complex has been modified in meiosis. In budding and fission yeast, a meiotic paralogue of Mcd1/Scc1, called Rec8, is required for meiotic sister chromatid cohesion and recombination. Fission yeast (but not budding yeast) also has a meiosis-specific paralogue of Scc3, called Rec11, which participates in similar functions to Rec8, but also in distinct functions (Krawchuk et al. 1999). Furthermore, a mammalian, testis-specific paralogue of Smc1, called Smc1β, has been identified, which could represent a meiosis-specific variant (Revenkova et al., personal communication).

Role of cohesin and related proteins in meiosis

REC8 was identified in fission yeast as a meiosis-specific gene involved in recombination (de Veaux et al. 1992),

Table 3. Examples of meiotic cohesion mutants: comparison of defects in meiotic sister chromatid cohesion, meiotic recombination and axial element/synaptonemal complex formation. (AI anaphase I, MI, metaphase I, N.D., not determined, RN recombination nodule)

Mutation (species)	Meiotic cohesion[a]	Meiotic recombination[a]	AE/SC morphology[a]
red1Δ (*S. cerevisiae*)	Missegregation of recombined chromosomes (1);) loss of arm cohesion before AI (2)	Reduction in DSB initiation (3) and crossovers and gene conversions (4)	No AEs, no SC (1)
mek1Δ (S. cerevisiae)	Loss of arm cohesion before AI (2)	Reduction in DSB initiation (3) and crossovers and gene conversions (5, 6)	Full-length AEs, but multiple, short stretches of SC (5)
mer1 (*S. cerevisiae*)	Missegregation of recombined chromosomes (7)	Reduction in DSB initiation (8) and crossovers and gene conversions (7, 8)[b]	Full-length AEs, but no SC (9)
med1-1 (*S. cerevisiae*)[c]	Missegregation of recombined chromosomes (10)	Reduction in crossovers and gene conversions (10)	Apparently normal SC (10)
dis1-1 and dis1-2 (*S. cerevisiae*)	Missegregation of recombined chromosomes (11); sister centromeres probably segregate equationally at AI (11)	Not defective (11)	N.D.
tam1/ndj1 (*S. cerevisiae*)	Missegregation of recombined chromosomes (12)	Defective crossover interference on small (12) but not larger (13) chromosomes	Delay in the formation of AEs (13) and SC (12, 13)
spo13-1 (*S. cerevisiae*)	Sister centromeres segregate equationally in a one division meiosis (14)	Not defective (14)	SC present in *spo12-1*, *spo13*-1 double mutant (15, 16)
smc3-42 (*S. cerevisiae*)	Loss of centromeric cohesion before MI (17)	DSBs: normally formed but hyperresected and probably not repaired at all (17)	No AEs, no SC (17)
rec8Δ (*S. cerevisiae*)	Loss of arm and centromeric cohesion before MI (17)	DSBs: normally formed but hyperresected and probably not repaired at all (17)	No AEs, no SC (17)
rec8-110 and rec8-Δ (*S. pombe*)	Loss of arm cohesion before MI (18); sister centromeres segregate equationally at AI (19)	Reduction in crossovers (20, 21, 22)	Linear elements: short stretches and aggregates (18, 22)
dy1 (*Zea mays*)	Male meiosis: loss of arm cohesion before MI; sister centromeres segregate equationally at AI (23, 24)	Not defective (23)	SC central region: slightly wider (25), prematurely disassembled (23)
dsy1 (*Z. mays*)	Loss of arm cohesion before MI (26)	Crossovers occur, frequency N.D. (26)	SC: incomplete; SC central region: slightly wider, less robust, and prematurely disassembled (26)
ord (alleles 1-12) (*D. melanogaster*)	Loss of arm and centromeric cohesion before MI (27, 28, 29, 30)	Reduction in crossovers (27, 29, 30)	N.D.
meiS332 (alleles 1-10) (*D. melanogaster*)	Loss of centromeric cohesion (28, 31, 32, 33)	Not defective (31, 32)	N.D.
spo76-1 (*Sordaria macrospora*)	Loss of arm and centromeric cohesion before MI (34, 35)	Strong reduction in late RNs (35, 36), but only slight reduction in Rad51/ Dmc1foci (35)	AEs: some segments thin and split, others of normal width and synapsed (34, 35)

[a] References: 1, Rockmill and Roeder (1990); 2, Bailis and Roeder (1998); 3, Xu et al. (1997); 4, reviewed by Mao-Draayer et al. (1996); 5, Rockmill and Roeder (1991); 6, Leem and Ogawa (1992); 7, Engebrecht et al. (1990); 8, Storlazzi et al. (1995); 9, Engebrecht and Roeder (1990); 10, Rockmill and Roeder (1994); 11, Rockmill and Fogel (1988); 12, Chua and Roeder (1997); 13, Conrad et al. (1997); 14, Klapholz and Esposito (1980); 15, Moens (1974); 16, Moens et al. (1977); 17, Klein et al. (1999); 18, Molnar et al. (1995); 19, Watanabe and Nurse (1999); 20, Ponticelli and Smith (1989); 21, de Veaux and Smith (1994); 22, Parisi et al. (1999); 23, Maguire (1978); 24, Maguire (1990); 25, Maguire et al. (1991); 26, Maguire et al. (1993); 27, Mason (1976); 28, Goldstein (1980); 29, Miyazaki and Orr-Weaver (1992); 30, Bickel et al. (1997); 31, Sandler et al. (1968); 32, Davies (1971); 33, Kerrebrock et al. (1992); 34, Moreau et al. (1985); 35, van Heemst et al. (1999); 36, Zickler et al. (1992)

[b] The gene conversion defect but not the crossing over defect of the *mer1* mutant can be completely restored by overexpression of *MER2* (7, 8)

[c] *med1-1* is an allele of the *DMC1* gene of *S. cerevisiae* (see Fig. 1)

assembly of linear elements (structures equivalent to axial elements of the SC), and sister chromatid cohesion (Molnar et al. 1995; Watanabe and Nurse 1999). An orthologous gene with similar functions was later discovered in budding yeast (Klein et al. 1999).

Rec8 is probably loaded onto the chromatin during premeiotic S-phase (Watanabe and Nurse 1999); in meiotic prophase of *Schizosaccharomyces pombe*, Rec8 is localised in foci all over the chromatin (Parisi et al. 1999), with the highest concentration around the centromeres (Watanabe and Nurse 1999). As meiosis I proceeds, the protein is gradually lost from the arms, but it persists at the centromeres until metaphase II. In *S. cerevisiae* (Klein et al. 1999), Rec8 lines meiotic prophase chromosomes along their length. At the end of prophase, most Rec8 is lost from the chromosome arms, while it persists at the centromeres until anaphase II, as in *S. pombe*. In *rec8Δ* mutants of *S. cerevisiae*, sister chromatids separate prematurely (i.e. before meiosis I) and then segregate randomly (not equationally). In budding yeast, Rec8 is thus required both for arm and centromeric cohesion during meiosis (compare Fig. 2D). In *rec8* mutants of *S. pombe*, sister chromatids also separate prematurely but then segregate equationally (Watanabe and Nurse 1999). In this species, Rec8 is thus required for maintenance of arm cohesion and the co-orientation of kinetochores at metaphase I but, in the absence of Rec8, sufficient cohesion is retained at the centromeres to allow the chromosomes to align in the spindle and undergo equational segregation (compare Fig. 2C). In budding yeast, Spo13 is responsible for the persistence of Rec8 at the centromeres until the metaphase/anaphase II transition (Klein et al. 1999), as we will discuss in more detail below.

Furthermore, *rec8* mutants of *S. pombe* and *S. cerevisiae* show profound defects in meiotic recombination (Table 3). In *rec8Δ* mutants of *S. cerevisiae*, meiotic DSBs appear with normal kinetics, but they persist and become more extensively resected than in wild type; mature recombinant DNA molecules are not formed (Klein et al. 1999). Rec8 is thus not required for initiation but for some later step in meiotic recombination. Because cohesins have a role in chromosome organisation and in recombination, the question remains to be answered whether *rec8* mutants are incapable of creating the right meiotic context for DSB repair, or whether they are unable to perform some step in the repair process itself, or both.

rec8 mutants are also deficient in linear element/AE formation (Table 3). In *rec8Δ* mutants of budding yeast (Klein et al. 1999) no AEs are formed, and Red1, an AE component, remains dispersed in numerous dots throughout the meiotic prophase nucleus without forming linear structures. In fission yeast, *rec8* mutants make only very short stretches of linear elements, while most linear element material is found in aggregates (Molnar et al. 1995; Parisi et al. 1999).

Rad21 and Mcd1/Scc1, the mitotic paralogues of Rec8 in fission and budding yeast, play less important roles in meiosis. In budding yeast (Klein et al. 1999), Mcd1/Scc1 is expressed in meiosis, but at much lower levels than Rec8. Unlike Rec8, Mcd1/Scc1 does not localise to chromosome cores. In *mcd1/scc1* mutants, meiotic chromosomes segregate with an almost wild-type level of fidelity. However, Mcd1/Scc1 still has some role in meiosis because spore viability is only 50% in *mcd1/scc1* mutants (Klein et al. 1999). In fission yeast (Watanabe and Nurse 1999), overexpression of Rad21 cannot restore the meiotic defects of *rec8* mutants. On the other hand, mitotically expressed Rec8 complements most defects of Rad21-deficient cells of *S. pombe*, albeit that mitotic chromosomes display a slight tendency to segregate reductionally in these cells. Apparently, Rec8 functions in a similar way to Rad21 but has acquired additional roles in meiosis that Rad21 cannot fulfil.

Other components of the mitotic cohesin complex have no meiotic paralogue and participate both in mitosis and meiosis (Tables 2, 3). Smc3, for instance, is involved in the same meiotic functions as Rec8, at least in budding yeast (Klein et al. 1999). Proteins that interact functionally with cohesins may also have a role in both mitosis and meiosis. An example is Spo76 of *Sordaria* and its *Aspergillus* homologue BimD, which are involved in mitotic chromosome disjunction and DNA repair (see above). In *Sordaria*, Spo76 is required for meiotic homologous recombination and AE formation (Moreau et al. 1985; Zickler et al. 1992; van Heemst et al. 1999). The *spo76-1* mutant, which shows regional defects in mitotic sister chromatid cohesion, displays partially split AEs in meiotic prophase (Table 3). The resemblance of the mitotic and meiotic defects of *spo76-1* mutants suggests that the Spo76 protein fulfils similar roles in both types of cell cycle by influencing the strength of cohesion. The same could be true for BimD, which is required for ascospore formation in *Aspergillus* (van Heemst, unpublished observations), and is thus possibly involved in meiosis.

In summary, the cohesin complex is active in meiosis in a modified form. In *S. cerevisiae*, at least one component (Mcd1/Scc1) is partially replaced by a meiosis-specific paralogue (Rec8), whereas in *S. pombe* two components are replaced, Rad21 (by Rec8) and Scc3 (by Rec11). In this modified condition, the cohesin complex functions in linear element/AE formation, meiotic recombination, arm cohesion, centromeric cohesion, and the reductional orientation of kinetochores (at least in fission yeast) at meiosis I.

It remains to be investigated to what extent these conclusions can be extrapolated to higher eukaryotes, in particular with respect to chromosome disjunction. There are some indications that cohesins may not persist along the chromosomes of higher eukaryotes during mitotic metaphase (Losada et al. 1998) (see above), and it remains to be established whether they persist along the arms of meiotic metaphase I chromosomes of these organisms, or whether other factors are responsible for cohesion. This could have implications for the regulation of disjunction. However, there is little reason to doubt that the role of cohesins in mitotic G2-phase (cohesion for recombination) is recruited in meiotic prophase (cohesion for homologous recombination) (see below).

Meiotic sister chromatid cohesion and axial element formation

At first sight, it seems unlikely that cohesin complexes would provide the basis for AE formation. Axial elements are single axial structures that are shared by both sister chromatids. In the mitotic cycle, such shared chromatid axes are not normally observed, and cohesin complexes are not normally seen in mitotic axial structures. However, under certain experimental conditions (cell cycle drugs in combination with a topoisomerase II inhibitor), single chromosomal axes supporting both sister chromatids appear in G2 of mitotically dividing mammalian cells (Gimenez-Abian et al. 1995). We propose that these single intersister axes contain cohesins and that similar single axes arise in meiotic prophase and provide the basis for AEs. There are various indications for this. Grasshopper spermatocytes in early diakinesis (i.e. immediately after AE disintegration) have one single silver-stainable core per homologue, which probably represents the still unseparated chromatid axes (Rufas et al. 1992). This single core differentiates into two cores (one per chromatid) during metaphase I. Furthermore, Smc1 and Smc3 are localised in dots along the AEs of rat SCs, and Smc1 interacts in vivo and in vitro with two AE components of the rat, Scp2 and Scp3 (Eijpe et al. 2000). Spo76 of *Sordaria*, which probably interacts functionally with cohesins (Table 2), is also localised along the AEs during meiotic prophase (van Heemst et al. 1999); *spo76–1* mutants assemble abnormal, partially split AEs (Table 3).

Axial element components, sister chromatid cohesion and recombination

In budding yeast, three meiotic proteins have been identified that localise along AEs: Red1, Mek1 (see Table 3) and Hop1. Red1 localises along meiotic chromosomes wherever AEs are present (Smith and Roeder 1997), whereas Mek1 is a functional kinase that also localises along meiotic prophase chromosomes and can phosphorylate Red1 (Bailis and Roeder 1998; de los Santos and Hollingsworth 1999). Two-hybrid analyses, studies of genetic interactions and co-immunoprecipitations provide ample evidence that these three proteins interact in vivo (see Hollingsworth and Ponte 1997; Smith and Roeder 1997; Bailis and Roeder 1998; de los Santos and Hollingsworth 1999; and references therein), and it seems likely that they cooperate in AE formation and functioning.

red1 mutants (see also Table 3) show a combination of defects that is very informative for the link between meiotic recombination, sister chromatid association and AE formation:

AEs are not detectable (Rockmill and Roeder 1990)

red1 mutants induce meiotic DSBs, albeit at reduced levels (about 25% of the wild-type level; Xu et al. 1997). Apparently, Red1 assists Spo11 in cleaving DNA without being absolutely necessary (Xu et al. 1997).

Double-strand breaks that are induced in *red1* mutants are converted into intersister JMs and interhomologue JMs, but the bias for the formation of interhomologue JMs has turned into an intersister bias; probably, the *red1* mutation abolishes an interhomologue-specific pathway, leaving behind a pathway in which interhomologue bias is absent (Schwacha and Kleckner 1997).

Part of the interhomologue JMs in *red1* mutants are resolved into crossovers, but these do not ensure proper disjunction of homologues at meiosis I (Rockmill and Roeder 1990). Nondisjunction of crossover chromosomes is indicative of a lack of arm cohesion at meiosis I (see Fig. 2). A defect in arm cohesion was also evident in fluorescent in situ hybridization experiments performed on pachytene nuclei of *red1* mutants (Bailis and Roeder 1998).

Centromeric cohesion is probably not affected in *red1* mutants because the spore inviability of *red1* mutants is rescued by the *spo13-1* mutation (Rockmill and Roeder 1988). If the *red1* mutation abolishes centromeric cohesion, one would expect that chromatids would segregate randomly in *spo13 red1* mutants. However, it is possible that Red1 is important for co-orientation of kinetochores in meiosis I.

red1 mutants bypass the so-called pachytene arrest, which is triggered by persistence of certain recombination intermediates and requires Mek1 as well as Red1 (Xu et al. 1997).

Red1 thus plays a pivotal role in meiotic chromosome behaviour. Probably, it forms the physical link between the protein complex that forms the DSBs, the (meiotic) cohesin complex and the AE, and co-ordinates recombination with chromosome behaviour and meiotic cell cycle progression.

Mek1 is a protein kinase that phosphorylates Red1 and depends for its chromosomal localisation on Red1 and Hop1 (Bailis and Roeder 1998). A small amount of Mek1 persists along the chromosomes until metaphase/anaphase I. *mek1* mutants show arm cohesion defects and bypass the pachytene arrest. These effects may arise through defective phosphorylation of Red1.

The *HOP1* gene was identified in a screen for mutants that can perform meiotic intrachromosomal recombination and are defective in interhomologue recombination (Hollingsworth and Byers 1989). *hop1* mutants induce meiotic DSBs, albeit at reduced levels (about 10% of the wild-type level) (Schwacha and Kleckner 1994). However, they form neither detectable heteroduplex DNA (Nag et al. 1995) nor interhomologue JMs and crossovers. They do form intersister JMs, but this is considerably delayed, as if a block on intersister interactions had to be relieved before intersister JMs could be formed (Schwacha and Kleckner 1994). In short, Hop1 functions in the context of the AE and is indispensable for meiotic interhomologue recombinational interactions.

Cohesion and recombination: meiosis versus mitosis

In Fig. 3 and below, we present a partially hypothetical comparison of the roles of cohesins in mitotic and mei-

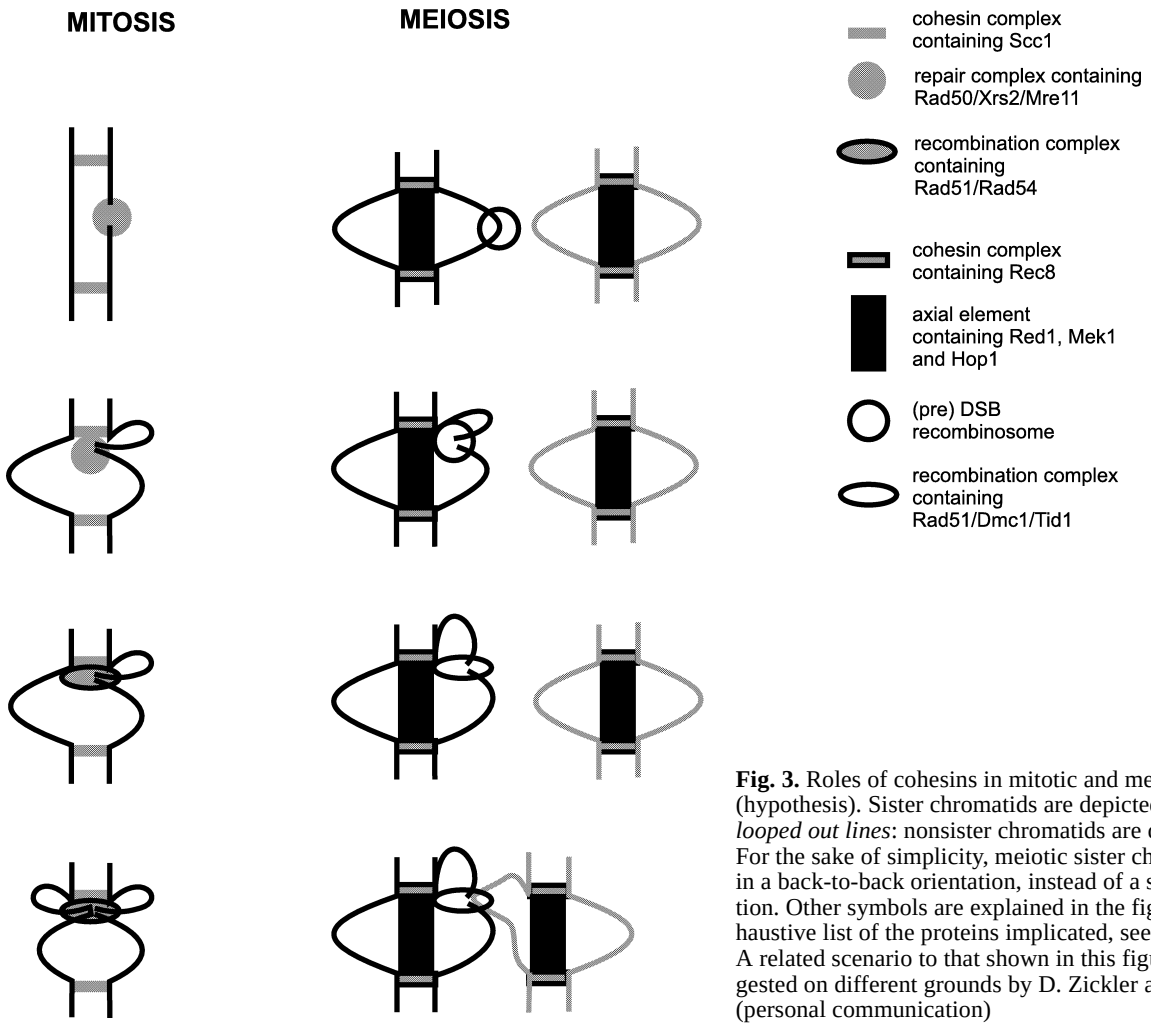

Fig. 3. Roles of cohesins in mitotic and meiotic recombination (hypothesis). Sister chromatids are depicted as *straight or looped out lines*: nonsister chromatids are differently *shaded*. For the sake of simplicity, meiotic sister chromatids are drawn in a back-to-back orientation, instead of a side-by-side orientation. Other symbols are explained in the figure. For a more exhaustive list of the proteins implicated, see Fig. 1 and the text. A related scenario to that shown in this figure has been suggested on different grounds by D. Zickler and N. Kleckner (personal communication)

otic cohesion and recombination, in order to provide an overview of the many gene functions involved.

Meiotic crossover formation versus mitotic recombinational repair: an hypothesis

We suppose that in mitotic G2 cohesins keep sister chromatids precisely aligned. If accidentally a DSB occurs, DNA repair proteins, including the Rad50/Xrs2/Mre11 complex, associate with the DNA ends and prepare them for repair. The protein complex containing the DSB is then transferred to the nearest cohesin complex, possibly through contact between Rad50 and Mcd1/Scc1. Cohesin plus the initial repair complex then attract other proteins of the DSB recombinational repair pathway (Fig. 1). Possibly, cohesin components assist these proteins in searching for homology in the corresponding segment of the sister chromatid and completing recombinational repair. Such a procedure would simplify homology search, avoid unequal sister chromatid exchanges and prevent all the problems of mitotic crossing over discussed above.

Meiotic prophase corresponds (roughly) to mitotic G2. We suppose that cohesin complexes ensure maintenance of sister chromatid cohesion, as in mitosis (see Fig. 3), but that in most complexes Mcd1/Scc1 has been replaced by Rec8. Presumably, the Rec8-containing cohesin complexes then serve as a basis for AE formation, whereas one possible difference between Rec8 and Mcd1/Scc1 function could be that Mcd1/Scc1-containing complexes cannot. Spread meiotic prophase nuclei of yeast *red1* mutants contain long “thin stained structures” with a stretched appearance (Rockmill and Roeder 1990). These could represent the still unseparated sister chromatid axes and contain cohesin complexes. In *red1* mutants of yeast (which do not assemble AEs), Rec8 still localises in rows of dots or thin elongated structures (Klein, personal communication); presumably, these correspond to the stretched, unseparated chromatid axes. Possibly, these Rec8-containing structures attract AE components (in budding yeast: Red1), so that short AE fragments arise (Padmore et al. 1991; Schwarzacher 1997), which later fuse to form full-length AEs. Meiotic recombination is not required for this because yeast *spo11* mutants can form full-length AEs (Loidl et al. 1994). DSBs are induced concomitantly with AE assembly (Padmore et al. 1991). The Rad50/Xrs2/Mre11 complex, together with other factors (Fig. 1), prepares the DSB site for double-strand DNA scission (Ohta et al. 1994) and possibly es-

tablishes contact with the nearest cohesin complex, which in most cases will contain Rec8 and will thus be associated with the AE. Cohesin plus (pre)DSB complex then attract additional proteins for homologous recombination as we supposed for mitotic recombinational repair. In higher eukaryotes, this has been beautifully visualised, first by demonstration of ultrastructurally recognisable protein complexes along AEs (early recombination nodules; reviewed in Carpenter (1988) and later by immunocytochemical localisation of various recombination proteins in early recombination nodules (Anderson et al. 1997) and along AEs (Bishop 1994; Terasawa et al. 1995; Ashley and Plug 1998). If the cohesin complex plus (pre)DSB complex contains Rec8 and is associated with an AE component (in budding yeast: Red1), homology search on the sister chromatid will be blocked, and the already assembled recombination complex has to search for another target. How contact is made with the homologous chromosome is not understood. In yeast, homologous chromosomes are already paired to some extent at the beginning of meiotic prophase (Weiner and Kleckner 1994); various mechanisms, including paranemic joints and alignment of heterochromatic blocks, might help roughly to align homologous chromosomes before DSBs are induced. For the interhomologue recombinational interactions, the yeast proteins Hop1 (see above) and Dmc1 (Schwacha and Kleckner 1997) are indispensable. Hop1 possibly stabilises initial recombination intermediates with the homologous chromosome, and limits resection of the 5′ ends (Kironmai et al. 1998). *hop1* mutants store meiotic DSBs in an unknown form and repair them later on the sister chromatid, presumably after Red1 has disappeared (Schwacha and Kleckner 1994). Once Hop1 has fulfilled its task (which still has to be defined), Mek1 regulates dissociation of Hop1 (Bailis and Roeder 1998), so that the recombination process can proceed and synapsis can follow.

To summarise the possible effects of cohesins on meiotic recombination (hypothesis): cohesin complexes containing Rec8 initiate AE formation by attracting Red1, Hop1 and Mek1. The cohesin complex can associate with the pre-DSB complex and attract proteins for further steps in homologous recombination, but homology search on the sister chromatid is blocked in the presence of Red1. Hop1 and Dmc1 are required for recombination with the homologue, and Mek1, in association with Red1, monitors progression of the recombination process (Xu et al. 1997) and relates this to the cell cycle through phosphorylation of Red1 (and possibly other proteins).

We propose that Mcd1/Scc1-containing cohesin complexes participate in a minor meiotic recombination pathway, which is more similar to mitotic recombinational repair. If, as seems likely (Klein et al. 1999), Mcd1/Scc1-containing complexes do not associate with Red1, this pathway should allow recombination with the sister chromatid. The Mcd1/Scc1-pathway could correspond to the “less differentiated pathway for meiotic recombination” postulated by Schwacha and Kleckner (1997). Defects in such a minor pathway could account for the reduced spore viability (50% of wild type) of *mcd1/scc1* mutants of budding yeast (Klein et al. 1999).

In higher eukaryotes, the relation between cohesion and meiotic recombination could be similar to that in yeast (see also Tables 2 and 3). A human orthologue of Rec8 has been identified and is expressed at high levels in the testis (Parisi et al. 1999). A possible homologue of Hop1 has been found in *Arabidopsis thaliana* (Caryl et al. 2000), and in *Caenorhabditis elegans*, where it localises along chromosome cores during meiotic prophase and meiosis I until the metaphase I-anaphase I transition (Zetka et al. 1999). A (functional) homologue of yeast Red1 has not yet been identified in other eukaryotes but Scp2 of the rat is a candidate (Offenberg et al. 1998), and phosphorylation of an AE component of the rat (Scp3) has been found (Lammers et al. 1995).

Meiotic versus mitotic chromosome disjunction

In meiosis, sister chromatid cohesion and recombinational repair have not only been recruited for crossover formation, but also for chromosome disjunction. This required adaptations at the chromosome level and the cell cycle level.

At the chromosome level, reciprocal recombination events have to be converted into crossovers of chromatid axes: chiasmata (Jones 1987). It is not known how this is accomplished. Probably, interhomologue recombination proceeds not only in association with the axis of the broken chromatid (as we suggest in Fig. 3), but also of the template chromatid. Breakage and reunion of DNA can then be linked directly to breakage and reunion of chromatid axes.

Furthermore, chromosome orientation depends in meiosis I on cohesion of chromatid arms only (Fig. 2A), whereas in mitosis, arm cohesion is relatively weak, and centromeric cohesion is far more important. Cohesion between meiosis I sister chromatids is mediated at least in part by cohesin containing Rec8 (Klein et al. 1999). In budding yeast, Mek1 persists on the chromosomes until the metaphase/anaphase I transition (Bailis and Roeder 1998), whereas in rat two AE components, Scp2 (Schalk 1999) and Scp3 (Moens and Spyropoulos 1995) persist in small amounts between the sister chromatids during meiosis I and possibly reinforce cohesion. Other proteins that might contribute to arm cohesion during meiosis I are the products of maize *DSY1* and *DY1* (Table 3) and as yet unidentified phosphoepitopes between metaphase I sister chromatids of grasshopper (Suja et al. 1999). The importance of arm cohesion distal to chiasmata is evident from the effect of crossover position on meiosis I chromosome disjunction: nondisjunction of human chromosome 21 at meiosis I is correlated with a more distal position of crossovers (Lamb et al. 1997).

At the cell cycle level, the timing of several events has changed to allow utilisation of cohesion and recombination for meiotic chromosome disjunction. In particular, the timing of sister kinetochore orientation, release of arm and centromeric cohesion and DNA synthesis have been adjusted to the two meiotic divisions (see above). In budding yeast, the *SPO13* gene plays a pivotal role in these adaptations.

Meiotic arm and centromeric cohesion depend on Rec8, which is related to Mcd1/Scc1 (see above; Klein et al. 1999). It therefore seems likely that release of arm cohesion in anaphase I and of centromeric cohesion in anaphase II requires Cdc20-activated APC, and involves scission of Rec8 and probably also Mcd1/Scc1. Other factors such as chromosome condensation and loss of phosphoepitopes between sister chromatids (Suja et al. 1999) possibly affect arm cohesion and enhance (but not trigger) its release in anaphase I.

Spo13 probably indirectly influences meiotic centromeric cohesion. In mitosis, overexpression of *SPO13* causes a block in G2-M. The arrested cells degrade Pds1 but not Mcd1/Scc1, and Spo13 therefore acts downstream of Pds1 in the regulatory pathway for release of cohesion (S. Prinz and A. Amon, personal communication). In meiosis I, Spo13 may have a similar effect and indirectly and temporarily protect Rec8 from cleavage by Esp1. The special conformation of the centromere (Tanaka et al. 1999) or the presence of specific centromeric factors such as *Drosophila* Mei-S332 and/or the absence of factors that affect arm cohesion (see above) might explain why protection is confined to the centromeric region. Another factor that may contribute to maintenance of centromeric cohesion during meiosis I is the co-orientation of sister kinetochores: this precludes one factor required for the release of centromeric cohesion, namely bipolar tension (Nicklas et al. 1995) between all sister kinetochores. However, co-orientation alone cannot ensure maintenance of centromeric cohesion through meiosis I: in *Drosophila*, the Mei-S332 protein appears on the centromeres at metaphase I (Moore et al. 1998) and is thus not involved in establishment of sister kinetochore co-orientation. In *mei-S332* mutants, centromeres fall apart immediately after meiosis I (Table 3), and Mei-S332 is thus required for protection of centromeric cohesion against effects that occur from metaphase I onwards (compare Fig. 2E). The yeast *DIS1* gene possibly also contributes to maintenance of centromeric cohesion through meiosis and mitosis (Rockmill and Fogel 1988) (Table 3).

Spo13 furthermore influences cell cycle progression. In mitosis, *SPO13* overexpression causes an arrest in G2-M by interfering with the M-phase promoting factor (MPF) pathway (McCarroll and Esposito 1994). In meiosis, *spo13-1* mutants perform a single division, as if meiosis I is skipped (Klapholz and Esposito 1980). In this single division, chromosomes segregate from almost exclusively equationally (Klapholz and Esposito 1980) to mixed reductionally and equationally (Hugerat and Simchen 1993). In wild type, Spo13 causes a delay in entering meiosis I, which possibly allows the cells to prepare their chromosomes for a reductional division. After meiosis I, Spo13 prevents full return to interphase, so that the cells enter a second division without an intervening S-phase. It has been suggested (McCarroll and Esposito 1994) that Spo13 achieves these effects by decreasing the rate at which transitions between different states of p34 kinase (which forms part of MPF) occur.

It is not known how Spo13 contributes to kinetochore co-orientation. Possibly, the Spo13-mediated delay in entering meiosis I allows the cells to co-orient the sister kinetochores. Analysis of a recently identified allele of *SPO13*, *spo13-23*, revealed that recombination can partially substitute for this aspect of Spo13 function. Recombination-proficient *spo13-23/spo13-23* diploid yeast cells perform two meiotic divisions and produce tetrads, like *SPO13/–* cells. In contrast, (recombination-deficient) *spo11/spo11 spo13-23/spo13-23* diploids perform one equational division, like *spo13-1/spo13-1* cells. Even recombination on a single chromosome affects the segregational behaviour of other chromosomes. Apparently, recombination events produce a diffusable signal that substitutes for the *spo13-23* defect with respect to centromeric cohesion and kinetochore co-orientation during meiosis I (L.H. Rutkowski and R.E. Esposito, personal communication). This would represent another aspect of the altered relationship between sister chromatid cohesion and recombination in meiosis.

Spo13 homologues have not been identified in other organisms. However, McCarroll and Esposito (1994) have pointed out that the vertebrate *c-MOS* oncogene might fulfil similar functions in meiosis to the yeast *SPO13* gene, albeit that the analogy is not perfect: c-Mos inhibits APC (Vorlaufer and Peters 1998), whereas Spo13 appears not to (S. Prinz and A. Amon, personal communication). Because meiosis is always embedded in a cellular developmental pathway (gametogenesis, sporogenesis), it is to be expected that many species-specific variations of the regulation of the meiotic cell cycle exist.

Conclusions

The discovery of the role of cohesins in meiotic recombination and sister chromatid cohesion reveals important connections between large diverse fields of research, covering recombination, DNA repair, mitosis and meiosis. It furthermore demonstrates the pivotal position of cohesins in the regulation of chromosome behaviour and DNA metabolism. Important topics to be investigated include the interactions engaged by cohesins and associated proteins in various states of the cell cycle and under various conditions of genotoxic stress. This will further elucidate the relation between the mitotic cycle and meiosis, and will provide numerous opportunities for connecting cytological observations with intracellular events at the DNA level and vice versa.

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