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Review Article

Meiotic Chromosome Interactions: Nonhomologous Centromere (Un)Coupling and Homologous Synapsis

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The fundamental function of meiosis, segregation of the maternal and paternal chromosomes, is facilitated by reciprocal recombination and intimate juxtaposition (synapsis) between the homologous chromosomes in meiotic prophase. Homolog synapsis, mediated by the synaptonemal complex (SC), is preceded by a stage of pairing between the centromeres of nonhomologous chromosomes. This pairing, named nonhomologous centromere coupling (NCC), depends upon the meiotic cohesin Rec8 and the SC protein Zip1. Nonhomologously coupled centromeres (NCCs), if remain tethered, must interfere with complete homolog synapsis (SC formation). Recent experiments demonstrate the existence of a mechanism that regulates NCC. Importantly, this is part of a regulatory network which couples dissolution of the NCCs with SC formation between the homologous chromosomes, thereby ensuring appropriate meiotic chromosome interactions. This paper reviews this network and presents speculations relating to the initiation of SC formation at centromere.

1. Introduction

Cell biologists working on meiosis, the cell division that segregates the maternal and paternal chromosomes to produce haploid gametes from diploid parent cells, have ever been fascinated by the ballet between chromosomes that occupy a substantial part of the meiotic prophase (reviewed in [1, 2]). This culminates into initial side-by-side alignment (named pairing) of the two homologous chromosomes, which subsequently converts to intimate physical juxtaposition (named synapsis) of the two homologs along their entire length. Synapsis between the homologous chromosomes is mediated by a complex proteinaceous structure named synaptonemal complex (SC). (SC may also form between nonhomologous chromosomes or segments of chromosomes that are not homologous.) The SC is a tripartite organelle in which a central element (CE) connects two lateral elements (LEs); each LE represents the merged axes formed along the length of the two sister chromatids (reviewed in [3]). In many organisms, homolog synapsis and SC formation are stringently coupled with the programmed induction of meiotic DNA double strand-breaks (DSBs) by the conserved topoisomerase Spo11, which initiates the process of reciprocal interhomolog recombination (reviewed in [4]).

A twist in the tale came from the Roeder laboratory [5]. It was demonstrated that, in budding yeast strain lacking Spo11, a stage of pairing, named Nonhomologous Centromere Coupling (NCC), between the centromeres of nonhomologous chromosomes precedes the homology-dependent synapsis. (The nonhomologously coupled centromeres will be referred as NCCs). Subsequent work enhanced understanding of the process [6–8]. NCCs are held together by the SC CE protein Zip1 whose stable association with the (peri)centromeric (and, also other chromosomal) sites depends upon the presence of the meiotic cohesin Rec8 (Figure 1). Importantly, it became clear that the eventual separation of the NCCs entails the same molecular signal (namely, programmed induction of meiotic DNA DSBs by Spo11) which also instigates the process of SC formation (Figure 1).

This paper discusses (1) the scenario that in budding yeast meiotic prophase, a regulatory network makes the appropriate interactions between the homologous chromosomes feasible, (2) the possible relationships between centromere coupling and SC formation and presents speculative models for the initiation of SC formation at centromere, (3) the likelihood that NCC is a wanton byproduct in meiosis.

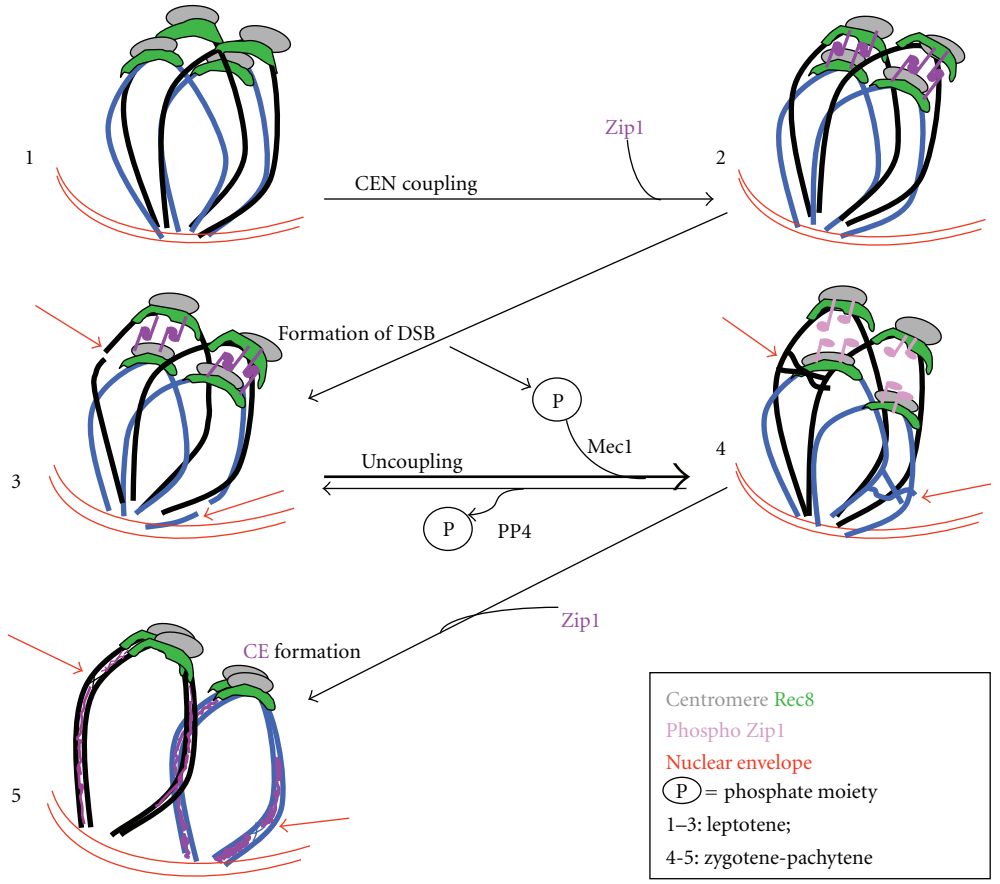

Figure 1: Schematic overview of nonhomologous centromere (*CEN*) coupling and synaptonemal complex (SC) formation in budding yeast meiotic prophase. Stable binding of Zip1 to the *CEN*s in Rec8-dependent manner leads to nonhomologous *CEN* coupling in early meiotic prophase (1, 2) [5–7]. *CEN* coupling is regulated by the phosphorylation-state of Zip1 owing to Mec1 kinase and PP4 phosphatase activities [8]. Spo11- catalyzed DNA DSBs (red arrows in 3) trigger Mec1 activity leading to Zip1-phosphorylation and uncoupling of the nonhomologous *CEN*s (4). DSB-induced crossover recombination (red arrows in 4, 5) initiates formation of the central element (CE) of SC between the homologous chromosomes (5). Though Mec1 and PP4 activities are likely in equilibrium in presence of DNA DSBs, Mec1-catalyzed uncoupling of the nonhomologous *CEN*s is shown here as the driven direction (thick arrow linking 3 and 4) since, in wild-type meiosis, recombination and subsequent SC formation between the homologous chromosomes stabilize and sequester the homologous *CEN*s from cycle of coupling-uncoupling [5, 8]. Two pairs of homologous chromosomes (black and blue) are shown. For simplicity, only one chromatid per chromosome is shown. Lateral elements of SC and Rec8 on chromosome arms are not shown. Chromosome ends are clustered and attached to the nuclear membrane.

2. Posttranslational Modification of Zip1 and Chromosome Interaction

In budding yeast, Zip1 is a meiosis-specific protein with long coiled-coil and terminal globular head domains, which forms homodimers. The C termini of the homodimers attach to the chromosome axis and two such homodimers from the pairing homologs interact at their N termini to form tetramers which constitute the fundamental unit of the CE of SCs [9–11].

Zip1-mediated chromosome interactions are positively regulated by its associations with small ubiquitin-like proteins, SUMO, or SUMO-conjugated proteins (also see later). Zip1 has a SUMO binding motif [12] which is required for its interaction with Red1-SUMO, an interaction that appears to trigger SC assembly [13, 14].

Zip1 is also the (potential) substrate of at least three different kinases, namely, the ATR-like serine/threonine kinase Mec1, the aurora B kinase Ipl1, and the cyclin-dependent kinase Cdc28 [8, 15–17]. Mec1-dependent phosphorylation of Zip1 triggers disengagement of NCCs (see later). Ipl1 activity on the other hand promotes timely disassembly, as measured by the immunofluorescence staining pattern of Zip1, of SC [16]. In simple model, phosphorylation by these kinases may modulate Zip1's ability to self-interact (e.g., [8]) and/or Zip1's (and/or its associated protein's) interaction with other axis-associated proteins (e.g., [16]), thereby destabilizing Zip1-mediated meiotic chromosome interactions. The polo-like kinase Cdc5 is required for SC disassembly [18–20]; the contribution of its kinase activity in this process is unclear, but appears distinct from that of Ipl1 [16]. By contrast, inhibition of the Cdc28 kinase activity prevents

normal CE formation; however, CE formation is probably independent of Cdc28-dependent phosphorylation of Zip1 [17].

3. Regulation of Centromere (Un)Coupling

NCCs represent a stage preceding homolog synapsis [5, 7]; therefore, if not timely uncoupled, they must interfere with complete SC formation between the homologous chromosomes. Further, cells with NCCs constitute a predominant prophase population in *spo11* mutant meiosis but a relatively minor population in wild-type meiosis; this indicates that the uncoupling depends upon some function of Spo11 (the alternate possibility that Spo11 inhibits coupling in wild-type meiosis is less likely since haploid *SPO11* cells forced to enter meiosis exhibit NCC [5, 8]). Recent work has provided important insight into this regulation and implicated Mec1-dependent phosphorylation of Zip1 as an essential aspect [8].

Hochwagen's laboratory identified that the amino terminus of Zip1 has a consensus site at serine 75 for Mec1 [8]. Mec1 seems to phosphorylate Zip1-S75 in vivo in DNA DSB-dependent manner. The group also identified the protein phosphatase, PP4, which counteracts Mec1-dependent phosphorylation of Zip1. Most interestingly, elimination of PP4 function by deleting a gene that codes for one of the PP4 subunits caused loss of NCC, and mutant *mec1* restored coupling in the *pp4* mutant.

Are Mec1-dependent phosphorylation of Zip1 and the loss of NCC in *pp4* mutant causally related? The answer is affirmative: a nonphosphorylable *zip1-S75A* mutant almost completely rescued the coupling defect of *pp4* mutant, whereas a phosphomimetic *zip1-S75E* allele disrupted coupling in otherwise wild-type (PP4) meiosis. In vitro Mec1-dependent phosphorylation of Zip1 has not been demonstrated; however, the genetic evidence collectively implies that NCC is regulated by the phosphorylation status at Zip1-S75 which is determined by a regulatory circuitry of Mec1 and PP4 (Figure 1). As the authors pointed out, S75 phosphorylation might prime phosphorylation at other Zip1-sites by yet unidentified kinases.

What triggers Zip1 phosphorylation? Available evidence suggests that the generation of meiotic DSBs, and/or the ensuing recombination intermediate(s), is essential. Loss of NCC in *pp4* mutant meiosis is rescued by active-site mutant *spo11*, and hyperphosphorylation of Zip1 seen in *pp4* mutant is abolished in both *mec1* and *spo11* active-site mutants [8].

4. Coupling of SC Formation with Nonhomologous Centromere Uncoupling

NCCs, if remained uncoupled, would interfere with SC formation between the pericentromeric sites of the homologous chromosomes. Thus NCCs must be uncoupled prior to, or simultaneously with, initiation of interhomolog SC formation. Coupling both these processes to programmed meiotic DSB formation reflects cell's cunning way to deal with the complexity (Figure 2).

Previous work in budding yeast and many (but, not all) other organisms showed that SC formation is stringently coupled with Spo11-induced meiotic DNA DSB formation and consequent interhomolog recombination. Budding yeast mutants with little or no Spo11 enzymatic activity only rarely form some SCs, whereas mutants defective in successive stages of recombination show coordinate defects in SC assembly [4]. DSBs per se are not sufficient to initiate SC formation, and earlier studies suggested that, in organisms where SC formation is coupled with recombination, SC formation initiates preferentially at sites of crossover-designated recombination (reviewed in [21]) and in budding yeast and other organisms requires a group of proteins collectively named as ZMM proteins ([26], reviewed in [22]). Some of the ZMM proteins are also named as SIC (for synapsis initiation complex) proteins. The SIC/ZMM group includes at least eight proteins including the SC CE component Zip1, and recruitment of Zip1 to the crossover-designated sites and its subsequent polymerization into CE depends upon physical interaction between the SIC/ZMM proteins and also between recombination proteins and (one or maybe more of) the SIC/ZMM proteins.

Surprise came subsequently. Later work in budding yeast implicated centromeres, despite the rarity of DNA DSBs and interhomolog recombination at these chromosomal sites [27–31], as additional prominent sites for initiation of SC formation. The initial report that tiny stretches (reflecting probable initiating events) of SCs often have centromeres at one end led to the proposal that centromeres are sites of SC initiation [5]. The result was differently interpreted [21] to suggest that centromere might serve as barrier to SC polymerization. However, consistent with the initial proposal, careful immunofluorescence analysis of SC initiation in wild-type meiotic prophase at a very early stage (zygotene) demonstrated that about half of the SC initiation sites are centromeric [23, 25]; probable SC initiating events were captured by analyzing tiny stretch of Zip1 associated with a single Zip2 immunostaining focus (Zip2 is a SIC/ZMM protein required for SC polymerization). In the previous immunofluorescence analyses, centromeric initiation was gone unnoticed owing to the absence of centromeric markers (e.g., [32–35]) and probably also due to progressively larger contribution of the crossover sites as meiosis progressed. Furthermore, Zip3 (one of the SIC proteins), which was thought to be recruited to the meiotic chromosomes by interaction with recombination proteins [33] at the sites of crossovers (e.g., [34]) to initiate the process of synapsis, is now shown also to localize in DSB-independent manner to the centromeres in early zygotene [23].

How the conundrum between the stringent recombination-dependency and the centromeric initiation of SC formation in budding yeast is solved? The Roeder laboratory came up with an answer: SC initiation at the centromeres can occur only after (normally) Spo11 catalyzed DSB formation elsewhere in the genome [25]. This trans DSB-dependency is ensured by the actions of two proteins: Zip3 and a prolyl isomerase Fpr3. These two proteins inhibit SC initiation specifically at the centromeres, apparently in a "checkpoint-like" manner, until meiotic DNA DSBs are induced. Together Fpr3 and Zip3 ensure that, despite coupled centromeres' potential to instigate extensive SC formation, no SC initiation

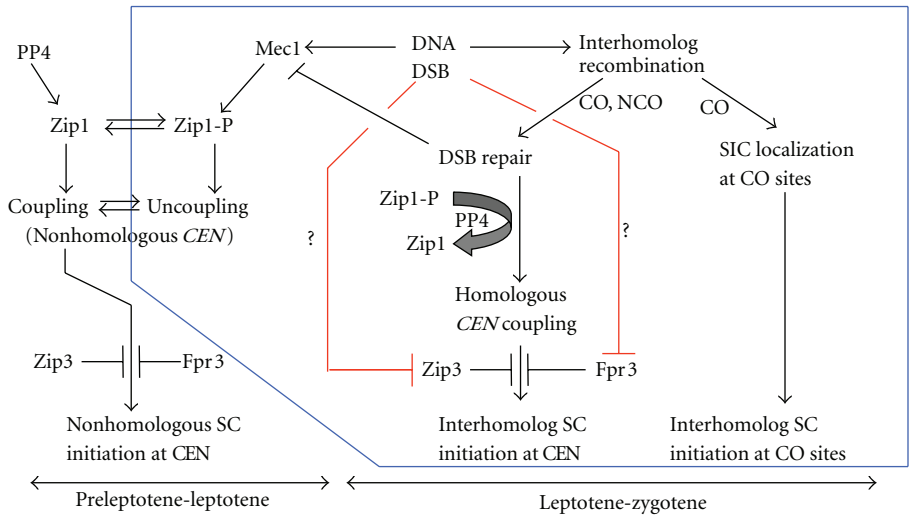

Figure 2: Spo11-induced meiotic DNA double-strand breaks (DNA DSBs) couple uncoupling of nonhomologous centromere (*CEN*) pairs with SC formation between homologous chromosomes, in budding yeast meiosis. *CEN* coupling and uncoupling depend upon the phosphorylation state of Zip1, respectively, regulated by the PP4 phosphatase and Mec1 kinase activities. Nonhomologous *CEN*s are coupled in early meiosis (leptotene), prior to Spo11-induced generation of DSBs. DSB-dependent activation of Mec1 and resultant Zip1-phosphorylation (Zip1-P) lead to uncoupling of the nonhomologous *CEN*s [8]. By this stage, coupling and uncoupling are likely in dynamic equilibrium [5, 8]. DSBs are repaired by crossover (CO) or noncrossover (NCO) recombination pathways. Interhomolog CO recombination leads to the localization of Synapsis Initiation Complex (SIC) at the sites of CO and consequent SC-initiation from the CO sites, in zygotene [21, 22]. CO recombination and SC formation between the homologous chromosomes may sequester the homologous *CEN*s from cycles of coupling-uncoupling and facilitate Zip1-dependent coupling of the homologous *CEN*s [23, 24], owing to PP4 activity and inhibition of further Mec1 activation. In addition to the CO sites, coupled *CEN*s, both homologous and nonhomologous, are potent sites of SC initiation [23, 25]. SC initiation from the nonhomologously coupled *CEN*s is prevented by the combined actions of Zip3 and Fpr3 which probably act in separate pathways [25]. Inhibition of the centromeric SC initiation by Zip3 and Fpr3 is relieved upon DNA DSB formation, the mechanism of which is unclear, allowing SC initiation from the homologously coupled *CEN*s. Steps in red are postulated. Steps inside the blue box are largely absent in *spo11* mutant. Note that the relationship between SC initiations at the centromere and at CO site is unclear, and alternate models are proposed in Figure 4.

takes place from the NCCs. Absence of both Fpr3 and Zip3 in *spo11* mutant leads to extensive SCs, formation of which initiate almost exclusively from the NCCs.

How meiotic DSB signaling overcomes the inhibitory effects of Fpr3 and Zip3 and how Zip3 exerts opposing effects on SC initiations at centromeric versus crossover sites are yet unclear.

5. Relationship between Coupling and Centromeric SC

Is Zip1-mediated coupling between the centromeres a prerequisite for the initiation of SC formation at the centromere? Intuitively, coupled centromeres would provide a platform for the subsequent interaction between Zip1 molecules from pairing chromosomes, but a nearby interhomolog recombination might also provide similar platform by holding the two centromeres close enough. A recent observation can be useful for experimentation. Despite being deficient in NCC, phosphomimetic *zip1-S75E* mutant forms apparently normal SC (unpublished data in [8]). It is possible that in *zip1-S75E*, owing to the absence of coupling between the homologous centromeres, centromeric SC initiation is reduced or abolished, and pericentromeric SC forms by polymerization from the nearest crossover sites (Figure 3(a)). Alternately, coupling of the centromeres is not a prerequisite, and the mere presence of Zip1 at the centromere is sufficient, for centromeric SC initiation (Figure 3(b)). According to this model, a *zip3* mutant, despite being proficient in stable Zip1 binding to the core centromere as revealed by chromatin immunoprecipitation [24], is defective in coupling between the centromeres of two homeologous (and possibly, homologous) chromosomes [24, 36], since it is deficient in polymerization of Zip1 from the centromeres some extent of which is required for efficient coupling. (Also see [36] for an alternate view based on their result that Zip1 bound less to the centromere in *zip3* mutant in immunofluorescence experiment. Gladstone et al. [24] present an altogether different view.) The model has the drawback that, at least in the case of NCC, coupling does not require Zip3 and SC [5, 6]. The model imposes an additional complexity: Zip3 is required to mediate two contrasting roles at the centromere (also see [23]): first, to inhibit SC initiation until meiotic DSBs are made and interhomolog recombination is initiated (see earlier), and second to promote SC polymerization afterward (as it does for SC initiation at crossover sites). The model however could explain the contrasting results that *zip3* mutant reduces stable Zip1 localization to the homeologous centromeres in an immunofluorescence assay [36] but not in a chromatin immunoprecipitation assay that

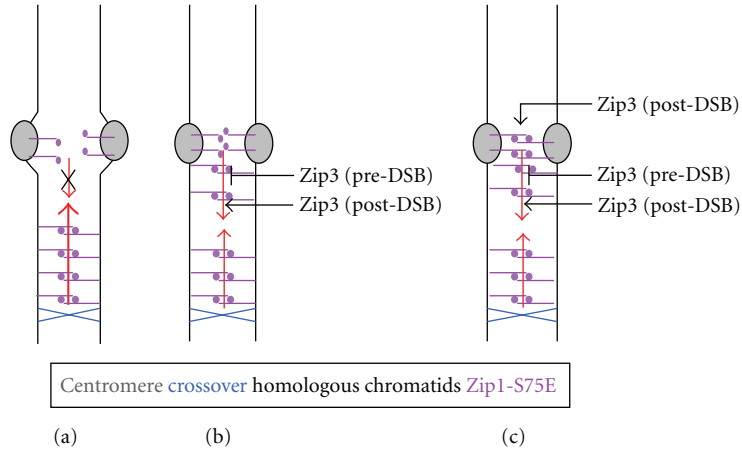

Figure 3: Schematic of possible effects of zip1-phosphomimetic mutant (e.g., *zip1-S75E* [8]) on the Zip1-mediated coupling between homologous *CEN*s and the centromeric SC formation. (a) Coupling between the homologous *CEN*s is disrupted which, in turn, inhibits SC initiation from the *CEN*s. Pericentromeric SC will be eventually formed by polymerization of Zip1 from the proximal crossover site (thick red arrow). (b) Coupling between the homologous *CEN*s, but not centromeric SC initiation, is disrupted. Zip1 polymerization initiates from the *CEN* bound Zip1. Note that the homologous *CEN*s appear to pair due to the secondary consequence of centromeric SC formation. (c) Zip1-dependent coupling between the homologous *CEN*s, which is promoted also by Zip3, is unaffected. Additionally, Zip3 exerts two opposing effects on centromeric SC initiation (both (b) and (c)). Before DSB formation and crossover (CO) recombination, Zip3 inhibits centromeric SC initiation [25]. After DSB formation and initiation of meiotic recombination, Zip3 promotes centromeric SC initiation. A pair of homologous chromosomes, for simplicity each with one chromatid is shown. SC formation in one arm is shown. Lateral elements of SC and Rec8 are not shown. The direction of SC formation is shown by red arrows. A single CO per homologous pair is shown.

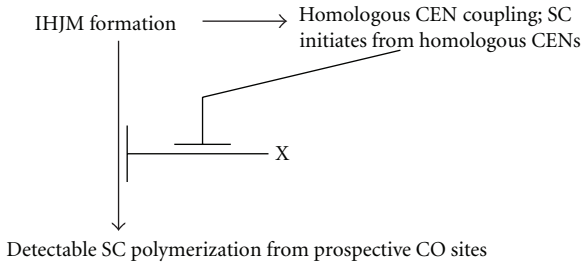

Figure 4: Possible events associated with the initiation of synaptonemal complex (SC) formation. Formation of recombinational joint molecules between the homologous chromosomes (interhomologue joint molecule, IHJM) enables stable coupling between the homologous *CEN*s and triggers centromeric SC initiation. This restrains an unknown inhibitory signal, X, which hitherto blocked SC initiation from the prospective CO sites.

detected binding nearly to the core centromeres [24]. A third scenario is, unlike NCC, Zip1-mediated coupling of the homologous centromeres [23, 24] is unaffected by serine75 phosphorylation (Figure 3(c)), and the two processes are distinct (as reflected by their different genetic requirements, see earlier). It is possible that, for NCC, Zip1 residues in the N terminal head domain that are dispensable for SC CE formation are critical [8], whereas hom(e)ologous centromere coupling occurs by Zip1-Zip1 interaction that is more similar to the interaction involved in CE formation [11]. The second and third models have overlapping features; the critical difference between them lays in the assumption that Zip3, in addition to, and independent of, its role in SC formation, modulates the ability of Zip1 to form tethers between the hom(e)ologous centromeres. It is yet unknown whether absence of Zip3 affects Zip1-mediated coupling between the homologous centromeres.

6. Centromeric SC Initiation: Added Complexity

The finding that centromeres represent majority of the SC initiation sites in very early zygotene (see earlier) raises conceptual issues. Do these SCs represent nonhomologous synapsis from the NCCs? If so, they must be disassembled to allow complete SC assembly between the homologous chromosomes [23]. This would probably involve regulatory signaling from recombinational interhomolog joint molecules and/or from homologous SC assembly. However, when two homologous centromeres labeled with green fluorescent protein were used to analyze the early centromere-associated SCs, they appeared to form between the homologous chromosomes (unpublished data in [23]).

If the early centromere-associated SCs are homologous, the question remains as to how (despite the infrequent interhomologue recombination) the homologous centromeres come into proximity to build a platform for the SC initiation? Conceivably, the centromeric SC initiation is associated with or assisted by coupling between the homologous centromeres (see earlier). Coupling will probably be preceded by a situation where the homologous chromosomes are stably connected by the formation of interhomolog joint molecules (IHJM), yet are unable to initiate detectable level of SC polymerization because of the existence of some inhibitory signal. Formation of the IHJM will facilitate locking of the homologous centromeres as Zip1-mediated couples,

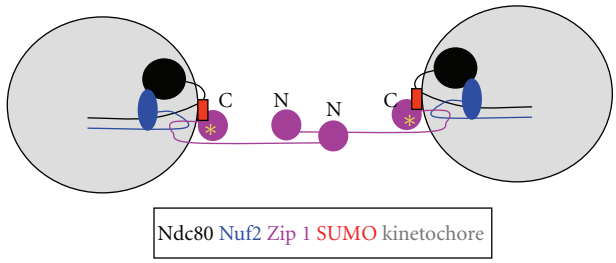

Figure 5: Schematic showing possible interactions of Zip1 with the meiotic kinetochore. The kinetochore protein Ndc80 is sumoylated [37, 38]. Zip1 is recruited by its direct physical interactions with Nuf2 (and/or Spc24, not shown) of the Ndc80 complex (e.g., [39, 40]) and then associates by its SUMO binding motif [12] with Ndc80-SUMO. Alternately, Zip1 may be recruited by its binding with Ndc80-SUMO, which then facilitates its interaction with other components of the Ndc80 complex. Since the putative SBM (residues 853–863 [13]) was not present in the Zip1 fragment used in the two hybrid screens [39], the second scenario is less likely. Interaction between the kinetochore-bound Zip1 promotes centromere coupling. Similar protein-protein interactions may also tether the two sister kinetochores in meiosis [41]. N and C represent the –NH2 and –COOH termini of Zip1. Yellow star represents the approximate location of SBM in Zip1. Chromosome arms are not shown.

sequestering them from the cycle of coupling-uncoupling; this subsequently will trigger the initiation of centromeric SC, which, in turn, will restrain the signal inhibiting SC polymerization from the prospective crossover sites (Figure 4).

7. How Zip1 Is Recruited to Centromere?

In budding yeast meiosis, Zip1 binding to centromeres is observed in both immunofluorescence and chromatin immunoprecipitation experiments [5–8, 24, 36]. How is Zip1 recruited to the meiotic centromere? Evidence suggests that Zip1's recruitment at the centromere is distinct from that at the crossover sites.

Crossover recombination and the SIC/ZMM proteins are essential for normal level of Zip1 recruit and CE formation in wild-type meiosis (see earlier). Immunofluorescence, coimmunoprecipitation and two-hybrid experiments have shown that Zip3 is an upstream player in this process which seems to be recruited at the crossover sites by its interaction with recombination proteins, and which then likely recruits other SIC/ZMM proteins (some of the SIC/ZMM proteins also exhibit interdependence for localization) including Zip2 and Zip1, promoting the latter's polymerization from the crossover sites [26, 32, 33, 35]. Biochemically, Zip3 is a putative E3 SUMO ligase which presumably sumoylates chromosomal proteins including the LE protein Red1 [12–14, 42]. Zip3-mediated covalent or noncovalent addition of SUMO to Red1 is proposed to trigger installation of the CE by promoting protein-protein interactions, for example, between Red1 and Zip1 [13, 14].

In early meiotic prophase, Zip1 foci, which presumably represent sites of NCCs, colocalize with SUMO conjugates [12]. SUMO staining of these Zip1 foci is Zip3 independent and is believed to depend upon other E3 ligases. In the same line, and in contrast to CE initiation at the crossover sites, both Red1 and the SIC/ZMM proteins Zip3 and Zip2 are dispensable for NCC [6] as well as for Zip1's stable association with the core centromere [6, 24]. The early zip3-independent SUMO staining foci also co-localize with topoisomerase II [12]. But it is not known whether topoisomerase II or other centromere-bound SUMO modified protein directly interacts with Zip1 in these foci or merely represents fortuitous colocalization, nor is it known whether topoisomerase II is required for NCC. Nonetheless, the disappearance, as observed in wild-type meiosis, of the early SUMO staining Zip1 foci is delayed when the SUMO deconjugating enzyme Ulp2 is mutated. This observation indicates that the (probably centromeric) recruitment [12] and/or stability of the early Zip1 foci depend upon SUMO. Is centromeric recruitment of Zip1 mediated by the kinetochore (see [43])? Pertinently, proteomic approach and sumoylation assays coupled with mutational analyses (e.g., [37, 38]) revealed that some of the bona fide kinetochore proteins, including Ndc80, are sumoylated in mitosis, conceivably by the Zip3-independent E3 ligase(s). The Ndc80 complex is an outer kinetochore complex of four proteins with coiled-coil and globular head domains (reviewed in [44]). The significance of the sumoylation with regard to kinetochore organization is largely unknown. Zip1 has a SUMO binding motif at its C terminus [12] which is required for its interaction with Red1 (in the context of SC), in a SUMO-dependent manner, in yeast two hybrid [13]. Furthermore, Zip1 interacts with two of the four proteins which assemble the Ndc80 complex, in two-hybrid experiments [39, 40]. Together these are intuitive. A reasonable scenario is that Zip1 is recruited to the meiotic kinetochore by its direct physical contact with some of the components of the Ndc80 complex, and thereafter the interface(s) is stabilized by SUMO-mediated interactions (Figure 5). Alternately, binding of SUMO/SUMO-conjugate to Zip1 promotes Zip1's interaction with, for example, Ndc80 resulting in kinetochore recruitment and stabilization by subsequent physical interaction(s) with other protein(s). Since the putative SUMO binding motif (residues 853–863, [12]) was absent in the Zip1 fragment used in the two hybrid screens [39], the second scenario is less likely. In addition to promoting centromere coupling and SC formation, Zip1's direct recruitment by the kinetochore may also ensure cosegregation of the sister chromatids in the first meiotic division by tethering the two sister kinetochores (see [41]).

8. Nonhomologous Centromere Coupling: Byproduct?

Centromeric associations, whose molecular basis is yet unclear, are observed in early meiosis in other organisms as well. But NCC has so far been experimentally demonstrated only in budding yeast. Thus, the issue of evolutionary conservation (which can be taken as an indication of probable functional significance) of NCC is far from settled.

Why does NCC exist in budding yeast? To explain the observed increase in centromere-proximal interhomolog

recombination in *zip1* mutant, probably at the expense of intersister repair [31], a model proposes that Zip1-mediated NCC might preclude deleterious recombination between the homologous centromeres by sequestering them with nonhomologous partners and thereby permitting repair of the DSBs only with the sister chromatids [7] (also see the reference for other proposed role of NCC). Though the model sounds attractive, a prediction of the model remains to be tested; the model would envisage similar effect in the centromere-proximal DSB repair in *rec8* mutant (Rec8 promotes Zip1-mediated NCC, see Section 1). Apparently consistent with the prediction, DNA analysis of meiotic recombination—intermediates has shown that Rec8 promotes bias to intersister repair in early meiosis (which is eventually counteracted by a barrier to intersister repair) [45]. But this effect is not specific to Rec8; the "mitotic" isoform of Rec8, Mcd1, if expressed in the place of Rec8, can substitute for Rec8 for this bias (Mcd1, however, cannot substitute for Rec8 for NCC [6]). Also, inconsistent with the prediction of the model, DNA analysis of meiotic DSB repair has shown that sister chromatid-based repair is efficient in *rec8* mutant, if the barrier to inter-sister repair (reviewed in [46]) is eliminated. This implies that Rec8 is not essential for inter-sister DSB repair [47]. Since the experiments used noncentromeric loci, it is presently unclear whether Rec8 is neutral to, or modulates, sister chromatid-based repair of DSBs near the centromere.

9. Zip1-Mediated Nonhomologous Chromosome Interactions: General Feature?

Are Zip1-mediated interactions between nonhomologous chromosomes restricted to the centromeres? In *spo11* mutant meiosis, Zip1 also localizes to Rec8-associated regions in the chromosome arms [6]. These DSB-independent chromosomal Zip1s in early meiosis might support association between the nonhomologous chromosome arms and intrachromosomal association, and Mec1 kinase might promote resolution of inappropriate meiotic chromosome interactions in general. However, since absence of both Fpr3 and Zip3 in *spo11* mutant almost always allow SC initiation apparently from the centromeres [25], the postulated Zip1-mediated inappropriate arm interactions may not be potent to initiate nonhomologous (and intrachromosomal) SC formation. Alternately, existence of mechanism to prevent recombination-independent SC initiation from Zip1-coupled nonhomologous arms is plausible.

Abbreviations

CE: Central element
CO: Crossover
DSB: Double-strand break
LE: Lateral element
NCC: Nonhomologous centromere coupling
NCCs: Nonhomologously coupled centromeres
SC: Synaptonemal complex.

Glossary

Centromere: The chromosomal site at which kinetochore assembles. Budding yeast centromeres consist of a 125 bp core DNA. Animal and plant centromeres are much larger and consist of megabases of DNAs.

Cohesin: The complex of proteins that establish a physical link between the sister chromatids during DNA replication. This physical link is called sister chromatid cohesion.

Crossover: Reciprocal exchange of corresponding sections between two homologous chromosomes by the process of recombination.

Homologous chromosomes: Two copies of each chromosome present in a diploid cell.

Kinetochore: The large protein complex that assembles generally at a specific site (centromere) of the chromosome and interacts with spindle microtubules during cell division to help chromosome segregation.

Meiotic synapsis: Intimate physical association of the (generally) homologous chromosomes by a proteinaceous structure called synaptonemal complex (SC). Within the SC, the axes of the two homologous chromosomes are ~100 nm apart.

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References

[1] G. S. Roeder, "Meiotic chromosomes: it takes two to tango," *Genes and Development*, vol. 11, no. 20, pp. 2600–2621, 1997.

[2] R. Koszul and N. Kleckner, "Dynamic chromosome movements during meiosis: a way to eliminate unwanted connections?" *Trends in Cell Biology*, vol. 19, no. 12, pp. 716–724, 2009.

[3] S. L. Page and R. S. Hawley, "The genetics and molecular biology of the synaptonemal complex," *Annual Review of Cell and Developmental Biology*, vol. 20, pp. 525–558, 2004.

[4] D. Zickler and N. Kleckner, "Meiotic chromosomes: integrating structure and function," *Annual Review of Genetics*, vol. 33, pp. 603–754, 1999.

[5] T. Tsubouchi and G. S. Roeder, "A synaptonemal complex protein promotes homology-independent centromere coupling," *Science*, vol. 308, no. 5723, pp. 870–873, 2005.

[6] A. Bardhan, H. Chuong, and D. S. Dawson, "Meiotic cohesin promotes pairing of nonhomologous centromeres in early meiotic prophase," *Molecular Biology of the Cell*, vol. 21, no. 11, pp. 1799–1809, 2010.

[7] D. Obeso and D. S. Dawson, "Temporal characterization of homology-independent centromere coupling in meiotic prophase," *PLoS ONE*, vol. 5, no. 4, Article ID e10336, 2010.

[8] J. E. Falk, A. C. H. Chan, E. Hoffmann, and A. Hochwagen, "A Mec1- and PP4-Dependent checkpoint couples centromere pairing to meiotic recombination," *Developmental Cell*, vol. 19, no. 4, pp. 599–611, 2010.

[9] M. Sym, J. A. Engebrecht, and G. S. Roeder, "ZIP1 is a synaptonemal complex protein required for meiotic chromosome synapsis," *Cell*, vol. 72, no. 3, pp. 365–378, 1993.

[10] K. S. Tung and G. S. Roeder, "Meiotic chromosome morphology and behavior in zip1 mutants of *Saccharomyces cerevisiae*," *Genetics*, vol. 149, no. 2, pp. 817–832, 1998.

[11] H. Dong and G. S. Roeder, "Organization of the yeast Zip1 protein within the central region of the synaptonemal complex," *Journal of Cell Biology*, vol. 148, no. 3, pp. 417–426, 2000.

[12] C. H. Cheng, Y. H. Lo, S. S. Liang et al., "SUMO modifications control assembly of synaptonemal complex and polycomplex in meiosis of *Saccharomyces cerevisiae*," *Genes and Development*, vol. 20, no. 15, pp. 2067–2081, 2006.

[13] F. M. Lin, Y. J. Lai, H. J. Shen, Y. H. Cheng, and T. F. Wang, "Yeast axial-element protein, Red1, binds SUMO chains to promote meiotic interhomologue recombination and chromosome synapsis," *EMBO Journal*, vol. 29, no. 3, pp. 586–596, 2010.

[14] C. S. Eichinger and S. Jentsch, "Synaptonemal complex formation and meiotic checkpoint signaling are linked to the lateral element protein Red1," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 107, no. 25, pp. 11370–11375, 2010.

[15] J. A. Ubersax, E. L. Woodbury, P. N. Quang et al., "Targets of the cyclin-dependent kinase Cdk1," *Nature*, vol. 425, no. 6960, pp. 859–864, 2003.

[16] P. Jordan, A. Copsey, L. Newnham, E. Kolar, M. Lichten, and E. Hoffmann, "Ipl1/Aurora B kinase coordinates synaptonemal complex disassembly with cell cycle progression and crossover formation in budding yeast meiosis," *Genes and Development*, vol. 23, no. 18, pp. 2237–2251, 2009.

[17] Z. Zhu, S. Mori, H. Oshiumi, K. Matsuzaki, M. Shinohara, and A. Shinohara, "Cyclin-dependent kinase promotes formation of the synaptonemal complex in yeast meiosis," *Genes to Cells*, vol. 15, no. 10, pp. 1036–1050, 2010.

[18] R. K. Clyne, V. L. Katis, L. Jessop et al., "Polo-like kinase Cdc5 promotes chiasmata formation and cosegregation of sister centromeres at meiosis I," *Nature Cell Biology*, vol. 5, no. 5, pp. 480–485, 2003.

[19] A. Sourirajan and M. Lichten, "Polo-like kinase Cdc5 drives exit from pachytene during budding yeast meiosis," *Genes and Development*, vol. 22, no. 19, pp. 2627–2632, 2008.

[20] G. A. Brar, A. Hochwagen, L. S. S. Ee, and A. Amon, "The multiple roles of cohesin in meiotic chromosome morphogenesis and pairing," *Molecular Biology of the Cell*, vol. 20, no. 3, pp. 1030–1047, 2009.

[21] K. A. Henderson and S. Keeney, "Synaptonemal complex formation: where does it start?" *BioEssays*, vol. 27, no. 10, pp. 995–998, 2005.

[22] A. Lynn, R. Soucek, and G. V. Börner, "ZMM proteins during meiosis: crossover artists at work," *Chromosome Research*, vol. 15, no. 5, pp. 591–605, 2007.

[23] T. Tsubouchi, A. J. MacQueen, and G. S. Roeder, "Initiation of meiotic chromosome synapsis at centromeres in budding yeast," *Genes and Development*, vol. 22, no. 22, pp. 3217–3226, 2008.

[24] M. N. Gladstone, D. Obeso, H. Chuong, and D. S. Dawson, "The synaptonemal complex protein Zip1 promotes bi-orientation of centromeres at meiosis I," *PLoS Genetics*, vol. 5, no. 12, Article ID e1000771, 2009.

[25] A. J. MacQueen and G. S. Roeder, "Fpr3 and Zip3 ensure that initiation of meiotic recombination precedes chromosome synapsis in budding yeast," *Current Biology*, vol. 19, no. 18, pp. 1519–1526, 2009.

[26] M. Shinohara, S. D. Oh, N. Hunter, and A. Shinohara, "Crossover assurance and crossover interference are distinctly regulated by the ZMM proteins during yeast meiosis," *Nature Genetics*, vol. 40, no. 3, pp. 299–309, 2008.

[27] E. J. Lambie and G. S. Roeder, "Repression of meiotic crossing over by a centromere (CEN3) in *Saccharomyces cerevisiae*," *Genetics*, vol. 114, no. 3, pp. 769–789, 1986.

[28] E. J. Lambie and G. S. Roeder, "A yeast centromere acts in cis to inhibit meiotic gene conversion of adjacent sequences," *Cell*, vol. 52, no. 6, pp. 863–873, 1988.

[29] F. Baudat and A. Nicolas, "Clustering of meiotic double-strand breaks on yeast chromosome III," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 94, no. 10, pp. 5213–5218, 1997.

[30] J. L. Gerton, J. DeRisi, R. Shroff, M. Lichten, P. O. Brown, and T. D. Petes, "Global mapping of meiotic recombination hotspots and coldspots in the yeast *Saccharomyces cerevisiae*," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 97, no. 21, pp. 11383–11390, 2000.

[31] S. Y. Chen, T. Tsubouchi, B. Rockmill et al., "Global analysis of the meiotic crossover landscape," *Developmental Cell*, vol. 15, no. 3, pp. 401–415, 2008.

[32] P. R. Chua and G. S. Roeder, "Zip2, a meiosis-specific protein required for the initiation of chromosome synapsis," *Cell*, vol. 93, no. 3, pp. 349–359, 1998.

[33] S. Agarwal and G. S. Roeder, "Zip3 provides a link between recombination enzymes and synaptonemal complex proteins," *Cell*, vol. 102, no. 2, pp. 245–255, 2000.

[34] K. A. Henderson and S. Keeney, "Tying synaptonemal complex initiation to the formation and programmed repair of DNA double-strand breaks," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 101, no. 13, pp. 4519–4524, 2004.

[35] T. Tsubouchi, H. Zhao, and G. S. Roeder, "The meiosis-specific Zip4 protein regulates crossover distribution by promoting synaptonemal complex formation together with Zip2," *Developmental Cell*, vol. 10, no. 6, pp. 809–819, 2006.

[36] L. Newnham, P. Jordan, B. Rockmill, G. S. Roeder, and E. Hoffmann, "The synaptonemal complex protein, Zip1, promotes the segregation of nonexchange chromosomes at meiosis I," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 107, no. 2, pp. 781–785, 2010.

[37] C. Denison, A. D. Rudner, S. A. Gerber, C. E. Bakalarski, D. Moazed, and S. P. Gygi, "A proteomic strategy for gaining insights into protein sumoylation in yeast," *Molecular and Cellular Proteomics*, vol. 4, no. 3, pp. 246–254, 2005.

[38] B. Montpetit, T. R. Hazbun, S. Fields, and P. Hieter, "Sumoylation of the budding yeast kinetochore protein Ndc10 is required for Ndc10 spindle localization and regulation of anaphase spindle elongation," *Journal of Cell Biology*, vol. 174, no. 5, pp. 653–663, 2006.

[39] J. R. Newman, E. Wolf, and P. S. Kim, "A computationally directed screen identifying interacting coiled coils from *Saccharomyces cerevisiae*," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 97, no. 24, pp. 13203–13208, 2000.

[40] J. Wong, Y. Nakajima, S. Westermann et al., "A protein interaction map of the mitotic spindle," *Molecular Biology of the Cell*, vol. 18, no. 10, pp. 3800–3809, 2007.

[41] A. Bardhan, "Complex regulation of sister kinetochore orientation in meiosis-I," *Journal of Biosciences*, vol. 35, no. 3, pp. 485–495, 2010.

[42] G. W. Hooker and G. S. Roeder, "A role for SUMO in meiotic chromosome synapsis," *Current Biology*, vol. 16, no. 12, pp. 1238–1243, 2006.

[43] A. Bardhan, "Many functions of the meiotic cohesin," *Chromosome Research*, vol. 18, pp. 909–924, 2010.

[44] C. Ciferri, A. Musacchio, and A. Petrovic, "The Ndc80 complex: hub of kinetochore activity," *FEBS Letters*, vol. 581, no. 15, pp. 2862–2869, 2007.

[45] K. P. Kim, B. M. Weiner, L. Zhang, A. Jordan, J. Dekker, and N. Kleckner, "Sister cohesion and structural axis components mediate homolog bias of meiotic recombination," *Cell*, vol. 143, no. 6, pp. 924–937, 2010.

[46] M. Pradillo and J. L. Santos, "The template choice decision in meiosis: is the sister important?" *Chromosoma*, vol. 120, no. 5, pp. 447–454, 2011.

[47] T. L. Callender and N. M. Hollingsworth, "Mek1 suppression of meiotic double-strand break repair is specific to sister chromatids, chromosome autonomous and independent of Rec8 cohesin complexes," *Genetics*, vol. 185, no. 3, pp. 771–782, 2010.