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Synapsis-Defective Mutants Reveal a Correlation Between Chromosome Conformation and the Mode of Double-Strand Break Repair During *Caenorhabditis elegans* Meiosis

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ABSTRACT

SYP-3 is a new structural component of the synaptonemal complex (SC) required for the regulation of chromosome synapsis. Both chromosome morphogenesis and nuclear organization are altered throughout the germlines of *syp-3* mutants. Here, our analysis of *syp-3* mutants provides insights into the relationship between chromosome conformation and the repair of meiotic double-strand breaks (DSBs). Although crossover recombination is severely reduced in *syp-3* mutants, the production of viable offspring accompanied by the disappearance of RAD-51 foci suggests that DSBs are being repaired in these synapsis-defective mutants. Our studies indicate that once interhomolog recombination is impaired, both intersister recombination and nonhomologous end-joining pathways may contribute to repair during germline meiosis. Moreover, our studies suggest that the conformation of chromosomes may influence the mode of DSB repair employed during meiosis.

DURING meiosis, chromosomes undergo programmed DNA double-strand breaks (DSBs) generated by the conserved topoisomerase-like protein Spo11 (Bergerat *et al.* 1997; Keeney *et al.* 1997). The existence of a conserved enzymatic function set in place to generate DSBs in fungi, plants, and animals underscores the significance of undergoing recombination during meiosis. Specifically, the reciprocal exchange of DNA that occurs during crossover recombination, after formation of programmed meiotic DSBs, is important for genetic diversity given that meiosis results in the formation of haploid gametes required for sexual reproduction. However, crossover recombination is also essential to establish physical attachments between homologous chromosomes during prophase, allowing for their proper subsequent alignment and accurate segregation to opposite sides of the spindle at meiosis I.

The importance of meiotic DSB formation and crossover recombination have led to intense studying of the various components and mechanisms operating in this process (for reviews, see Paques and Haber 1999; Zickler and Kleckner 1999; Keeney 2001). However, far less is known about the effects of chromosome configuration in DSB repair. Therefore, we exploited the existence of two different *syp-3* (synapsis defective) alleles with distinct differences both in the nuclear organization and conformation of chromosomes throughout prophase to investigate how changes in chromosome configuration interface with the progression of meiotic recombination.

In an accompanying article (Smolikov *et al.* 2007, this issue), we report the identification of *syp-3*, which encodes for a structural component of the central region of the synaptonemal complex (SC) in *Caenorhabditis elegans*. The SC is a proteinaceous structure that forms between paired and aligned homologous chromosomes during meiosis from yeast to mammals. It is composed of a pair of lateral elements assembled along the axes of a pair of homologous chromosomes, interconnected by transverse filaments that form the central region of this structure (Page and Hawley 2004). Our analysis of *syp-3* mutants revealed that SYP-3 restricts the loading of central region components of the SC promoting their assembly only in an appropriate context, bridging the axes of paired homologs. As a result, SYP-3 is required to stabilize homologous pairing interactions and for chiasma formation. However, we also uncovered differences in chromosome organization between a *syp-3* null (*ok758*) and C-terminal truncation (*me42*) mutants. Specifically, in the *syp-3* null mutant, as in *syp-1* and *syp-2* null mutants (MacQueen *et al.* 2002; Colaiácovo *et al.* 2003), SC formation is not observed by transmission electron microscopy (TEM), central region components SYP-1 and SYP-2 do not associate onto chromosomes, and chromosomes fail to redisperse upon entrance into pachytene, remaining instead in a clustered organization

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TABLE 1

Reduced crossover recombination in *syp-3* mutants

Genotype	Recombinant progeny	Total progeny	Map distance (cM)
+/(ok758 or +); dpy-3 unc-3/++	405 hermaphrodites	1407 hermaphrodites	35
+/(me42 or +); dpy-3 unc-3/++	238 hermaphrodites	901 hermaphrodites	32
ok758/ok758; dpy-3 unc-3/++	1 hermaphrodite 0 males	290 hermaphrodites 137 males	<0.3
me42/me42; dpy-3 unc-3/++	2 hermaphrodites 2 males	300 hermaphrodites 165 males	<0.8

Recombination analysis was performed as in Kelly *et al.* (2000).

until late pachytene. In the C-terminal truncation mutant, SC formation is also not observed by TEM analysis. However, SYP-1 and SYP-2 are observed associating with unsynapsed chromosomes once they redisperse in pachytene. Interestingly, chromosomes redisperse prematurely in this mutant compared to wild type, suggesting that association of central region components, albeit an incorrect association along unsynapsed chromosomes, may serve as a trigger for redispersal. Moreover, our analysis suggested that this association may effectively truncate or shorten the extent of time during which chromosomes search for homology, driving them out from the clustered organization and resulting in reduced pairing levels.

Here, we examined DSB repair in our *syp-3* mutants and observed that SYP-3 is required for crossover recombination given its requirement for appropriate synapsis between homologs. We also observed both sister chromatid-mediated recombination and nonhomologous end joining (NHEJ) operating in meiotic DSB repair once accessibility to a homologous partner or intersister recombination is respectively abrogated. Comparisons between different *syp-3* alleles support a model in which two temporal windows (one early, the other late) for DSB repair during prophase are tightly related to chromosome configuration and structural constraints. Altogether, our analysis revealed how DSB repair is modulated by changes in both chromosome organization and structural constraints resulting from alterations in the assembly of the central region of the SC.

MATERIALS AND METHODS

Genetics: *C. elegans* strains were cultured at 20° under standard conditions as described in brenner (1974). Bristol N2 worms were utilized as the wild-type background. The following mutations and chromosome rearrangements were used (Riddle *et al.* 1997; Dernburg *et al.* 1998; MacQueen *et al.* 2002; Colaiácovo *et al.* 2003; Martin *et al.* 2005; this article):

LGI: *syp-3(me42, ok758), hT2[bli-4(e937) qIs48] (I;III)*
LGIII: *lig-4(ok716)*
LGIV: *spo-11(ok79), nT1 [unc-?(n754) let-?(m435)] (IV, V)*
LGV: *syp-2(ok307), syp-1(me17)*
LGX: *dpy-3(e27) unc-3(e151)*

DAPI analysis and immunostaining: DAPI staining, immunostaining, and analysis of stained meiotic nuclei were carried out as in Colaiácovo *et al.* (2003) and as in Rogers *et al.* (2002). Antibodies were used at the following dilutions: α-RAD-51 (1:100) and α-REC-8 (1:100). Secondary antibodies used were: Cy3 anti-rabbit (Jackson Immunochemicals) at 1:200 and Alexa 488 anti-mouse (Molecular Probes, Eugene, OR) at 1:400.

RNA interference: Production of double-stranded RNA for *rec-8(RNAi)* and the RNAi procedure were carried out as described in Colaiácovo *et al.* (2003). REC-8 depletion was assayed by REC-8 antibody staining of whole mounted gonads and monitoring for oocytes carrying 24 univalents at diakinesis.

Time-course analysis for RAD-51 foci: Quantitation of RAD-51 foci was performed as described in Colaiácovo *et al.* (2003), except that all seven zones composing the divided germline were quantitated. The average number of nuclei scored per zone (n) for wild type, *syp-3(ok758), syp-3(me42), syp-3(me42); syp-2, syp-3(ok758); rec-8(RNAi), syp-3(me42); rec-8(RNAi), lig-4(ok716), syp-3(me42); lig-4(ok716), syp-3(me42); rec-8(RNAi); lig-4(ok716)* were: zone 1 ($n = 123$), zone 2 ($n = 128$), zone 3 ($n = 115$), zone 4 ($n = 135$), zone 5 ($n = 109$), zone 6 ($n = 90$), and zone 7 ($n = 79$).

RESULTS

SYP-3 is required for meiotic crossover recombination: Cytological analysis of germline chromosome morphology in both *syp-3* mutants revealed that in addition to altered chromosome morphogenesis and nuclear organization earlier in prophase, both carried 12 univalents instead of 6 bivalents in diakinesis oocytes (Smolikov *et al.* 2007 (accompanying article). Therefore, we examined whether this lack of chiasmata results from an inability to form crossovers. We measured crossover frequencies for a genetic interval spanning 80% of the X chromosome and observed a reduction to <0.9 and 2.5% of the wild-type level in *ok758* and *me42*, respectively (Table 1).

Formation and repair of DSBs in *syp-3* mutants: The lack of chiasmata and the severely reduced levels of crossover recombination observed in the *syp-3* mutants could reflect either an inability to form meiotic DSBs or an inability to repair DSBs as crossovers. To distinguish between these possibilities, we utilized an antibody against RAD-51 (a protein involved in DNA strand exchange during DSB repair; Sung 1994) and examined the levels of RAD-51 foci in nuclei throughout meiotic prophase (Figures 1 and 2). We observed that levels of RAD-51 foci rose upon entrance into transition zone (zones 2 and 3)

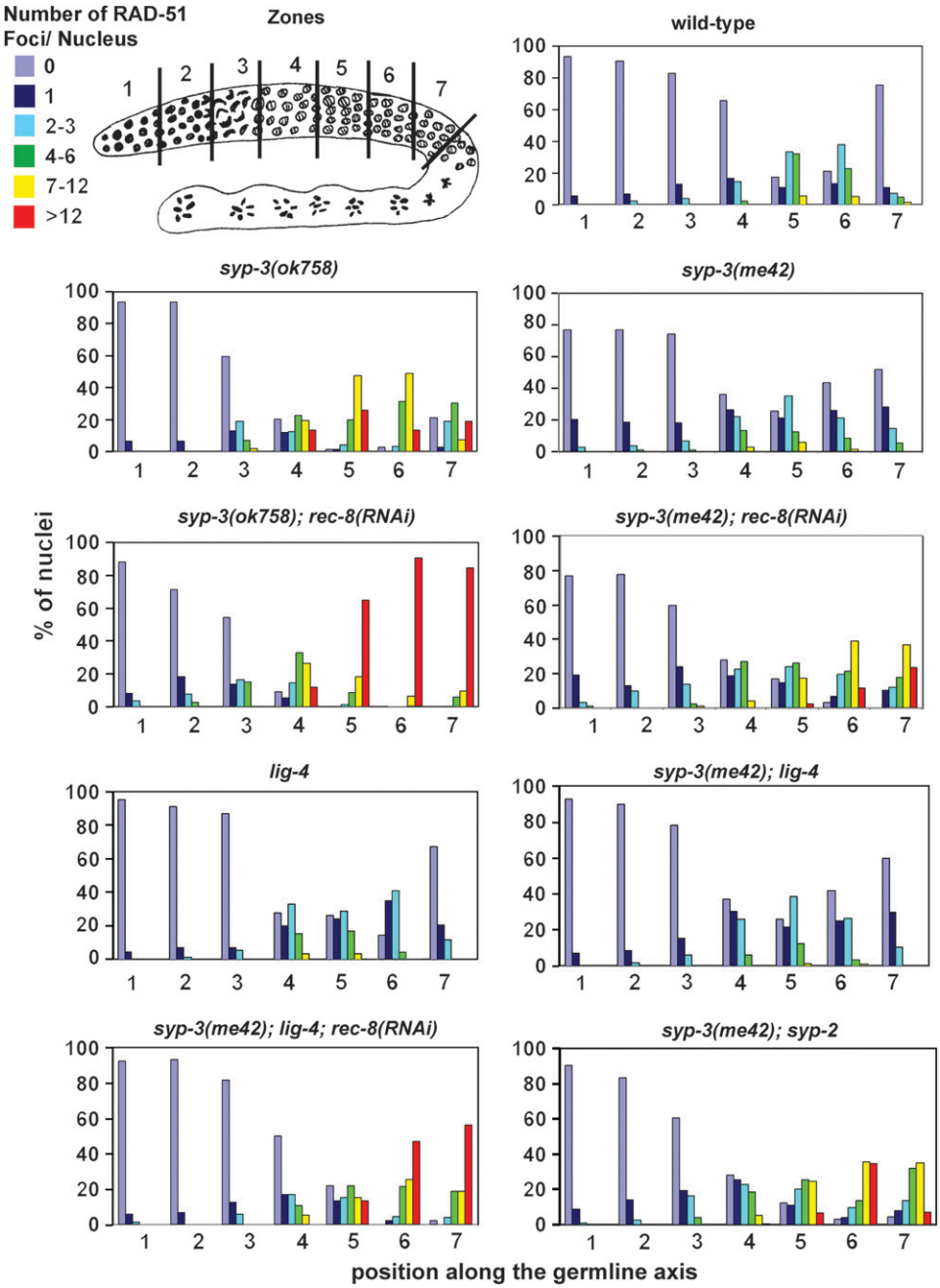

FIGURE 1.—Quantitative time-course analysis of RAD-51 foci during meiotic prophase. Germline diagram indicates the zones along the germline throughout which RAD-51 foci were scored for all nuclei. Zone 1 and most of zone 2 consist of nuclei undergoing mitotic divisions (premeiotic tip). Zone 3 consists of nuclei entering meiosis (transition zone). Zones 4–7 consist of nuclei in early through late pachytene. Levels of observed RAD-51 foci are indicated by the color code. Histograms depict the quantitation of RAD-51 foci in germlines of the indicated genotypes. Positions along the *x*-axis correspond to the zones along the germline as indicated in the diagram. The *y*-axis indicates the percentage of nuclei falling into each corresponding category indicated by the color code.

in both *syp-3* mutants with wild-type kinetics, indicating that SYP-3 is not required for the initiation of meiotic recombination.

Analysis of nuclei in early and mid-pachytene (zones 4 and 5) revealed that levels of RAD-51 foci were higher at these stages in *syp-3(ok758)* than in wild type and remained elevated throughout late pachytene. While only 13% of nuclei still bear more than one RAD-51 focus by late pachytene (zone 7) in wild type, 61% carry more than one focus in *syp-3(ok758)*. Furthermore, RAD-51 foci persisted in nuclei upon entrance into diplotene (one to two foci per nucleus), a stage at which RAD-51 foci are no longer observed in wild type. This result suggests that SYP-3 is required for the proper progression of recombination. Meanwhile, in *syp-3(me42)*, both the levels of RAD-51 foci throughout prophase and the kinetics of foci formation and disappearance closely paralleled those observed in wild type. Moreover, RAD-51 foci were not present in diplotene nuclei in *syp-3(me42)*. This suggests that DSBs are being repaired with near-wild-type efficiency in *syp-3(me42)*, although repair is not resulting in crossovers.

We also examined the levels of germ cell apoptosis observed in *syp-3* mutants (Table 2). Previous studies have shown that late pachytene nuclei undergo apoptosis triggered by unrepaired meiotic DSBs that are sensed as DNA damage (GARTNER *et al.* 2000). Utilizing the levels of germ cell corpses observed in late pachytene as

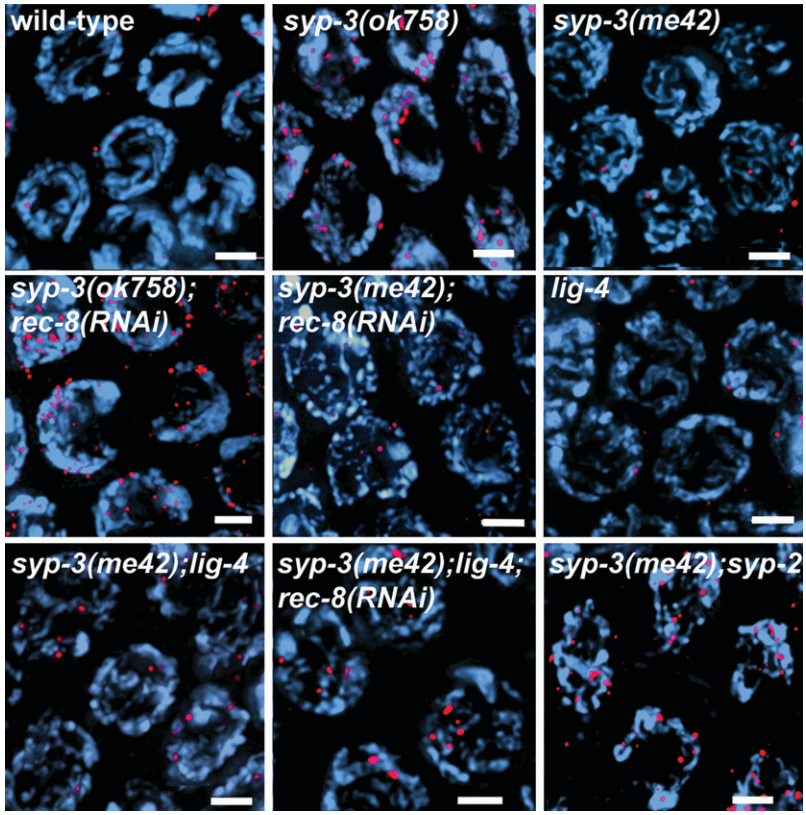

FIGURE 2.—Sister chromatid-mediated recombination and NHEJ are alternative modes of meiotic DSB repair in *syp-3* mutants. Elevated levels of RAD-51 foci are apparent in *syp-3(ok758)* and further accentuated if sister chromatid cohesion is disrupted in *syp-3(ok758); rec-8(RNAi)*. In *syp-3(me42)*, levels of RAD-51 foci are comparable to wild-type, *lig-4*, or *syp-3(me42); lig-4*. However, they are elevated in *syp-3(me42); lig-4; rec-8(RNAi)* and in *syp-3(me42); syp-2*. Images are projections halfway through 3D data stacks of mid-pachytene (zone 5) nuclei. DAPI-stained chromosomes (blue); α-RAD-51 (red). Bars, 2 μm.

a readout, we observed a 4.5-fold increase in *syp-3(ok758)* compared to either age-matched wild-type worms or *spo-11* worms where the initiation of meiotic DSB formation is abrogated. This increase is similar to that observed in the *syp-1* and *syp-2* mutants, where levels of RAD-51 foci also remain elevated throughout late pachytene (MACQUEEN *et al.* 2002; COLAIÁCOVO *et al.* 2003). Meanwhile, levels of germ cell apoptosis were not as significantly increased in *syp-3(me42)* compared with either wild type or *spo-11*. This suggests that in *syp-3(ok758)*, DSBs are either failing to be repaired or are engaging in aberrant intermediates leading to germ cell apoptosis via the activation of a pachytene DNA damage checkpoint. In contrast, DSB repair is more effective in *syp-3(me42)*, resulting in lower levels of germ cell corpses.

To further examine the correlation between DSB repair, chromosome configuration, and structural constraints, we assessed progression of meiotic recombination via immunostaining of RAD-51 in *syp-3(me42); syp-2* double mutants (Figures 1 and 2). In contrast to *syp-3(me42)* single mutants, in *syp-3(me42); syp-2* double mutants, chromosomes remain in a clustered organization instead of redispersing prematurely and SYP proteins no longer associate with chromosomes, similar to *syp-1*, *syp-2*, and *syp-3* null mutants (Figure 2; MACQUEEN *et al.* 2002; COLAIÁCOVO *et al.* 2003; SMOLIKOV *et al.* 2007, accompanying article). Whereas in *syp-3(me42)*, disappearance of RAD-51 foci occurs with near wild-type kinetics, in *syp-3(me42); syp-2*, DSB repair is no longer completed by late pachytene (zone 7), with RAD-51 foci persisting through early diplotene (one to three foci per nucleus). Moreover, levels of RAD-51 foci per nucleus are elevated and resemble those observed for either *syp-2* or *syp-3(ok758)*. These results suggest that either progression into a dispersed configuration and/or SYP-1 and SYP-2 loading, even if along unsynapsed chromosomes, can promote DSB repair throughout early and mid-prophase.

TABLE 2

Germ cell apoptosis in *syp-3* mutants

Genotype	Mean no. of germ cell corpses ± SE
Wild-type	1.81 ± 0.12
spo-11(ok79)	1.6 ± 0.22
syp-1(me17)	8.94 ± 0.67
syp-3(ok758)	8.25 ± 0.43
syp-3(me42)	2.54 ± 0.21

Germ cell corpses were scored in adult hermaphrodites 20 hr post-L4 as in KELLY *et al.* (2000). Between 32 and 134 gonad arms were scored for each genotype. Statistical comparisons between genotypes were conducted using the two-tailed Mann-Whitney test. *syp-3(ok758)* differed significantly from wild type ($P = <0.0001$) and from *spo-11* ($P = <0.0001$) but did not differ significantly from *syp-1(me17)* ($P = 0.6254$). Meanwhile, *syp-3(me42)* differed significantly from both *syp-1(me17)* and *syp-3(ok758)* ($P = <0.0001$, $P = 0.0001$); however, it also differed, albeit to a much lesser extent, from either *spo-11* ($P = 0.0061$) or wild-type ($P = 0.0062$).

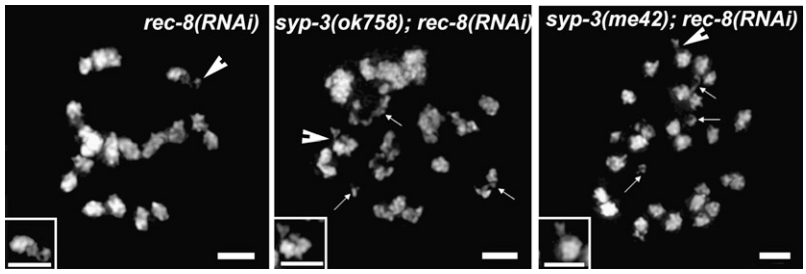

FIGURE 3.—Examining how changes in chromosome structure affect DSB repair. DAPI-stained oocytes at late diakinesis (projections encompass entire nuclei) are depicted. *rec-8(RNAi)* results in 24 separated sister chromatids with occasional fragments (indicated by arrowhead and enlarged in inset). In *syp-3(ok758); rec-8(RNAi)* and *syp-3(me42); rec-8(RNAi)*, more frequent chromosome fragmentation is observed, as indicated by arrows (arrowhead indicates example depicted at a higher magnification in the inset). In addition, chromosome aggregation is observed in *syp-3(ok758); rec-8(RNAi)*. Bars, 2 μm.

Evidence that both intersister recombination and NHEJ contribute to meiotic DSB repair when interhomolog recombination is impaired: The eventual disappearance of RAD-51 foci in *syp-3* mutants coupled with the production of viable progeny (~4%; SMOLIKOV *et al.* 2007, accompanying article) suggests that DSB repair occurs in *syp-3* mutants despite the absence of stable pairing between homologous chromosomes. Thus, we investigated the contribution of sister chromatid-directed repair by examining the consequences of depleting the meiotic cohesin REC-8 in *syp-3* mutants.

Depletion of REC-8 via RNAi in an otherwise wild-type background leads to the formation of 24 chromatid-sized DAPI-stained bodies and occasional fragments in diakinesis oocytes due to the inability of maintaining the attachments between the 12 pairs of sister chromatids (Figure 3; PASIERBEK *et al.* 2001). REC-8 depletion in either *syp-3* mutant did not alter the temporal progression of the nuclear reorganization characteristic of either single *syp-3* mutant. However, it resulted in the formation of 24 DAPI-stained bodies in addition to severe chromosome fragmentation. Some chromosome clumping was also observed in *syp-3(ok758); rec-8(RNAi)*. These results suggest that repair is occurring between sister chromatids rather than between homologous chromosomes in the *syp-3* single mutants. Moreover, quantitative analysis of RAD-51 foci in *syp-3(me42); rec-8(RNAi)* reveals significantly lower levels of RAD-51 foci during mid- and late pachytene in this background compared to *syp-3(ok758); rec-8(RNAi)* ($P < 0.0001$ for zone 6 by the two-tailed Mann-Whitney test, 95% C.I.; Figure 1 and supplemental Figure 1 at http://www.genetics.org/supplemental/). Specifically, 83–94% of all nuclei in mid-through late pachytene (zones 5–7) carry seven or more RAD-51 foci in *syp-3(ok758); rec-8(RNAi)*. This is similar to the 90–97% observed in *rec-8(RNAi)* (data not shown) but clearly different from the only 19–60% observed in *syp-3(me42); rec-8(RNAi)* throughout the same region. This last observation suggests that in addition to sister chromatid-mediated repair, chromosomes might be able to engage in additional modes of repair when they are dispersed as opposed to restrained in a clustered organization during early or mid-prophase.

To examine the contribution of NHEJ to repair in the *syp-3(me42)* mutants, we observed the levels of RAD-51 foci throughout meiotic prophase in a *syp-3(me42); lig-4* double mutant (ligase IV is involved in religating DNA ends during NHEJ; Figures 1 and 2). The levels of RAD-51 foci in *syp-3(me42); lig-4* followed a trend similar to that observed in either a *lig-4* or wild-type background, indicating that NHEJ does not play a primary role in meiotic DSB repair in *C. elegans*, consistent with previous studies (MARTIN *et al.* 2005; CLEJAN *et al.* 2006). However, the contribution of NHEJ to DSB repair becomes more evident when access to sister chromatids as a template for repair is no longer available. Thus, in a *syp-3(me42); lig-4; rec-8(RNAi)* background, levels of RAD-51 foci increased significantly in late pachytene compared to *syp-3(me42)*, *syp-3(me42); lig-4*, or *syp-3(me42); rec-8(RNAi)* mutants ($P < 0.0001$ for all pairwise combinations in zone 6, two-tailed Mann-Whitney test, 95% C.I.; Figure 1 and supplemental Figure 1 at http://www.genetics.org/supplemental/). Moreover, RAD-51 foci (one to three per nucleus) were still apparent in mid-diakinesis oocytes in *syp-3(me42);lig-4; rec-8(RNAi)* mutants, while they are no longer present at that stage in any of the other aforementioned backgrounds. Altogether, these results indicate that NHEJ can also contribute to meiotic DSB repair when homologous chromosomes are unavailable.

DISCUSSION

Relationship between chromosome organization and mode of DSB repair: Although the stable association between homologs is impaired in both *syp-3* mutants, these mutants differ in their kinetics of disappearance of RAD-51 foci, which may reflect differences in the timing and/or mode of repair. In the case of *syp-3(ok758)*, and similar to *syp-1* and *syp-2* null mutants, high levels of both RAD-51 foci and apoptosis are observed in late prophase, correlating with a persistent clustered organization of chromosomes. In contrast, in *syp-3(me42)*, a timely disappearance of RAD-51 foci and near wild-type levels of apoptosis correlates with chromosomes dispersing upon exit from transition zone. Moreover, in *syp-3(me42); syp-2* double mutants where chromosomes remain in an extended polarized nuclear organization, elevated levels of RAD-51 are observed in late prophase [once again similar to *syp-2* and *syp-3(ok758)* null mutants], supporting the idea that DSB repair correlates

with chromosome dispersal and loading of SC components. Together, these data raise the possibility that chromosome configuration (*i.e.*, clustered *vs.* dispersed) may affect the capacity for and/or timing of DSB repair. Under this scenario, the clustered organization would inhibit repair, whereas the dispersed organization would permit progression of repair.

Whereas the idea that progression of DSB repair is influenced by the clustered *vs.* dispersed state of the chromosomes accounts nicely for some aspects of our observations, it does not, however, readily explain all features of progression of DSB repair in the *syp-3* mutants. During wild-type meiosis, a barrier to sister chromatid repair is proposed to operate so that repair occurs between nonsister chromatids from homologous chromosomes (Hollingsworth *et al.* 1995; Schwacha and Kleckner 1997; Wan *et al.* 2004; Webber *et al.* 2004; Niu *et al.* 2005). However, in the *syp-3* mutants, given that DSBs are formed but homologs are not stably paired, interhomolog repair is also impaired. In *syp-3(ok758)* mutants, repair may occur in a delayed fashion when chromosomes finally redisperse in late pachytene and the relationship between sister chromatids is proposed to become less stringent (Colaiácovo *et al.* 2003). In *syp-3(me42)* mutants, the timing of disappearance of RAD-51 foci suggests that the barrier preventing sister chromatid recombination may be lifted prematurely. It is possible that in addition to promoting the dispersal of chromosomes, the inappropriate loading of SC central region proteins in the *syp-3(me42)* mutant also affects the relationship between sister chromatids in a manner that permits intersister recombination during early-mid prophase when interhomolog recombination is favored during wild-type meiosis. In the accompanying article (Smolikov *et al.* 2007), we demonstrated that some of the SYP-1 protein appears localized between sister chromatids in the *syp-3(me42)* mutant; this localization may allow it to function in promoting intersister recombination events.

The *syp-3(me42)* mutant has also enabled us to investigate the contribution of NHEJ to DSB repair in the germline. Although NHEJ is not a primary mode of repair in the germline (Martin *et al.* 2005; Clejan *et al.* 2006), NHEJ has recently been observed to participate in meiotic DSB repair in *brc-2* mutants where homologous recombination is impaired due to the misregulation of RAD-51 (Martin *et al.* 2005). In this work, we demonstrate that NHEJ can participate in germline DSB repair when both homolog-mediated and sister chromatid-mediated recombination are impaired due to synapsis defects and defective sister chromatid cohesion. This suggests that NHEJ may be simply outcompeted by interhomolog or intersister-mediated homologous recombination. Alternatively, NHEJ may be under regulatory constraints that are released concomitant with changes in chromosome configuration and structural constraints.

DSB repair does not drive early changes in chromosome configuration during *C.elegans* meiosis: Our studies are consistent with a model by which changes in chromosome configuration affect DSB repair progression. However, we also addressed whether the reverse also applied, which is whether DSB repair drives early changes in chromosome configuration during meiosis. While this is the case for budding yeast and Sordaria (Trelles-Sticken *et al.* 1999; Storlazzi *et al.* 2003), it does not seem to be the case in *C. elegans* (MacQueen *et al.* 2002; Colaiácovo *et al.* 2003; this article). First, the formation of DSBs *per se* is not required for chromosomes to acquire a polarized nuclear organization upon entrance into meiosis, for SC assembly between

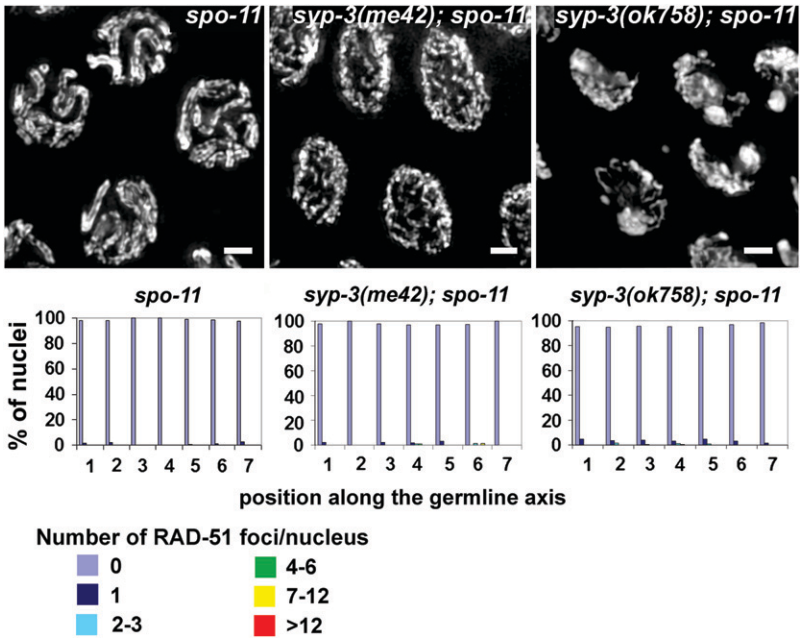

Figure 4.—Uncoupling the exit from a clustered organization from meiotic DSB formation. DAPI-stained mid-pachytene nuclei (projections are halfway through 3D data stacks). *syp-3(me42); spo-11* and *syp-3(ok758); spo-11* are indistinguishable from the corresponding *syp-3* single mutants. Bars, 2 μm. Histograms depict the quantitation of RAD-51 foci in germlines of the indicated genotypes (as described in Figure 1). The average number of nuclei scored per zone (n) for *spo-11*, *syp-3(me42); spo-11*, *syp-3(ok758); spo-11* were: zone 1 ($n = 138$), zone 2 ($n = 158$), zone 3 ($n = 145$), zone 4 ($n = 138$), zone 5 ($n = 127$), zone 6 ($n = 102$), and zone 7 ($n = 90$).

homologs or for redispersal of chromosomes upon progression into pachytene, as determined through the analysis of *spo-11* mutants (Dernburg *et al.* 1998). Second, in *syp-1*, *syp-2*, and *syp-3(ok758)* null mutants, chromosomes persist in a polarized nuclear organization that is not altered when meiotic DSB formation is abrogated in the absence of SPO-11 (Figure 4; MacQueen *et al.* 2002; Colaiácovo *et al.* 2003). Third, in the case of *syp-3(me42)*, the premature chromosome redispersal characteristic of this mutant is also not altered in a *syp-3(me42); spo-11* mutant (Figure 4). Fourth, while the levels of RAD-51 are increased in *syp-3(me42)*; *rec-8(RNAi)* double mutants compared to *syp-3(me42)*, the altered progression of DSB repair does not lead to a change in chromosome organization within the nuclei and chromosomes still redisperse prematurely as in *syp-3(me42)*. Therefore, initiation and/or progression of DSB repair are not directly driving early changes in chromosome configuration during meiosis. This is, however, distinct from a later wave of chromosome organization that is observed to occur between the early and late pachytene substages and that has been proposed to be under recombination-dependent regulation in *C. elegans* (Carlton *et al.* 2006).

In conclusion, SYP-3 is a novel SC component that plays a central role in the regulated formation of the SC central region between homologous chromosomes. Comparisons between different *syp-3* mutants are consistent with a model in which changes in chromosome configuration may modulate the mode and timing of DSB repair employed during prophase progression. Therefore, our findings support the view that a complex system of checks and balances acts to coordinate these processes to achieve a successful outcome of meiosis.

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