Heredity **82** (1999) 1–6 *Received 20 August 1998, accepted 24 September 1998*

Short Review

The relationship between synapsis and recombination: two different views

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Although remarkable advances in the understanding of the meiotic process have been achieved in the last few years, the relationship between pairing (alignment of homologous chromosomes), synapsis (intimate association of homologous chromosomes in the synaptonemal complex — SC) and recombination has not been precisely defined. Studies on budding yeast have challenged the traditional view of the SC as a structural support of the recombinational machinery as in yeast early steps in the recombination pathway not only precede SC formation but determine it. On these grounds, recombination should be required for synapsis. This review analyses the experimental evidence concerning the controversial relationship between synapsis and recombination.

Keywords: meiosis, meiotic nodules, recombination, synapsis, synaptonemal complex.

Introduction

Sexually reproducing eukaryotes maintain their chromosome number across generations by means of a special cell division called meiosis. In this process, four haploid germ cells are produced by two successive rounds of chromosome segregation that are not separated by DNA replication. At the first division, homologous chromosomes move to opposite poles. With respect to their origins (maternal and paternal gamete) and genetic content, the segregation of the centromeres and neighbouring regions (which extend to the first crossover points) is reductional. At the second division, the segregation of the centromeres is equational, as it is in mitosis, whereby the two sib-centromeres separate from each other and move to opposite poles. Fusion of gametes at fertilization restores the diploid chromosome number and initiates zygotic development.

To ensure meiotic segregation of a complete set of chromosomes at anaphase I, several structures that facilitate synapsis and recombination between homologues are required: the synaptonemal complex (SC) and the meiotic nodules (MNs). The SC is a meiosis-specific ribbon-like structure of proteinaceous nature consisting of a central element, two flanking lateral elements and linking transverse filaments (Moses, 1968; Heyting, 1996). In early prophase I, each chromosome develops an axial element between sister chromatids that is called a lateral element once homologous chromosomes synapse. The MNs are nucleoprotein complexes visualized by electron microscopy, and are postulated to contain enzymes required in the various stages of recombination. They are associated with the axial elements of the newly formed SCs in zygotene–early pachytene or with mature SCs in mid-late pachytene. The former (early MNs) seem to be involved in homology recognition while the latter (late MNs) indicate the positions where reciprocal recombination takes place (Carpenter, 1987; Plug *et al.*, 1998).

Molecular and enzymatic details of meiotic recombination coupled to classic cytological observations have converted the meiotic process, especially early prophase I stages, to a field of active research in the last few years. In particular, dramatic advances have been carried out using budding yeast, *Saccharomyces cerevisiae*, that have challenged some classical views on meiosis, especially the role of the SC in the process of recombination (Kleckner, 1996; Roeder, 1997). These results imply that SC is not essential for the initiation of recombination but recombination is required for synapsis initiation. It is difficult to concentrate many years of research on the relationship between synapsis and recombination in a few pages; therefore, this review is only an attempt to summarize the most relevant experimental evidence in order to show to a broad audience the present state of affairs.

The traditional view (synapsis–recombination)

The hypothesis that SC formation provides a framework for the initiation of crossing over has been mainly based on cytological observations that show that chiasmata occur only in chromosomal regions where a SC is formed (reviewed in Von Wettstein *et al.*, 1984; Loidl, 1994). It assumes that crossovers do not initiate until synapsis has been completed. General evidence for this view is as follows. (i) Some achiasmate organisms (e.g. male *Drosophila*; Meyer, 1964) do not assemble SCs. (ii) Mutants defective in synapsis are also defective in crossing over. This association has been described in many different species including plants, yeast and insects. For example, in the $C(3)G^{17}$ mutation which causes elimination of crossovers in female *Drosophila*, the lateral elements of the complex are absent (Rasmussen, 1975). (iii) Localized chiasmata are associated with localized synapsis. Five situations have been studied in detail, the flat-

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worm *Mesostoma ehrenbergii*, the boat-lily *Rhoeo spathacea* and the orthopteran species *Tetrix ceperoi*, *Mishtshenkotetrix brachyptera* and *Stetophyma grossum* (reviewed in del Cerro & Santos, 1997). In the former four species, distal chiasma localization and SC were restricted to the noncentromeric chromosome ends, while in *S. grossum* eight of the 11 bivalents showed extreme proximal chiasma localization and pericentromeric SCs. (iv) The distribution and frequency of late MNs, which are associated with the central region of the SC, are correlated with the distribution and frequency of chiasmata (reviewed in Carpenter, 1987). This pattern has been observed near the centromeres of *Allium fistulosum* and near the telomeres of the grasshopper *Chloealtis conspersa*. Likewise, an absence of localization of late MNs is observed in species that do not have localized chiasmata (Moens, 1994). (v) Evidence that the mean SC length at pachytene and the mean chiasma frequency at diplotene–metaphase I (or mean crossover frequencies) are correlated. These indications emerge from analyses of differences in SC length and chiasma or crossover frequencies between sexes (male vs. female), among individuals of the same sex (Jones & Croft, 1989; Quevedo *et al.*, 1997), or from analysing the effects of additional heterochromatin in meiocytes (Mogensen, 1977). In all cases, higher chiasma/crossover frequencies are associated with longer SCs.

The yeast view (recombination–synapsis–maturation of recombination products)

The view that the stage of commitment to crossing over might precede or accompany the full formation of the SC was already proposed by Maguire (1965, 1966, 1977) on the basis of the strong correlations found in maize heterozygotes between successful homologous synapsis of rearranged chromosome segments, and the occurrence of reciprocal exchange between them and the corresponding normal segments. Studies of meiosis in *S. cerevisiae*, especially those regarding to the chronology of the recombination pathway support this hypothesis. In this species, the earliest identifiable molecular event in meiotic recombination occurs after some form of homologous alignment (Weiner & Kleckner, 1994), and consists in the appearance of DNA double-strand breaks (DSBs). DSB formation is followed by the creation of joint DNA molecules which are the first chemically stable connections between the homologous chromosomes at the DNA level. Finally, heteroduplex DNA and mature recombination products appear (Smith & Nicolas, 1998). Temporal studies of synchronized yeast cultures show that DSBs appear early in prophase, prior to formation of mature SC, and disappear in zygotene as synapsis initiates. Joint molecules are present during pachytene, and recombination intermediates are resolved into either reciprocal (crossover) or nonreciprocal (gene conversion) events as the SC disassembles at the end of pachytene (Padmore & Kleckner, 1991). It must be taken into account that in gene conversion events a local DNA interaction is resolved without concomitant exchange of flanking markers (i.e. it is not visualized as a chiasma).

There are a few organisms such as *Aspergillus nidulans* and *Schizosaccharomyces pombe* in which high levels of genetic recombination are accomplished in the absence of a detectable SC (Egel-Mitani *et al.*, 1982; Bähler *et al.*, 1993). Several observations indicate that synapsis is also not required for recombination in budding yeast (reviewed in Roeder, 1997). (i) Mutants defective in DSB repair display defects in synapsis that are more severe in those mutants blocked at earlier steps in the repair pathway. (ii) Some mutants allow significant or even-normal levels of meiotic recombination (*red 1*, *mer 1*, *hop 1* and *zip 1*) but do not form SCs. For both *red 1 and mer 1* mutants, crossover events do not ensure correct segregation at anaphase I. (iii) The occurrence of ectopic recombination events (between homologous sequences on nonhomologous chromosomes) supports the notion that strand exchange takes place through a genome-wide homology search and is not dependent on the formation of the SCs (Engebrecht *et al.*, 1990).

These data are consistent with a model based on the dependence of synapsis on recombination. Synapsis would be initiated at the sites of meiotic recombination events and the formation of the SC would help to convert the recombination intermediates into crossing overs. The recent identification of a meiosis-specific protein (Zip 2) essential for SC formation, which colocalizes with proteins involved in DSB formation and processing, concurs with this hypothesis (Chua & Roeder, 1998).

Is recombination required for synapsis in higher eukaryotes?

Zygotene observations

Most detailed observations on zygotene complements have been carried out in plant chromosomes perhaps due to a superior stainability of their axial elements compared to animals. In different plant species zygotene is characterized by multiple association sites where axial elements show a regular alternation of divergence and convergence. These convergences, or association sites, frequently have nodules associated with them, and occasionally short pieces of central element occupy the space between the axial elements (see for instance Hasenkampf, 1984; Stack & Anderson, 1986; Albini & Jones, 1987; Anderson & Stack, 1988). These observations may be interpreted, according to the yeast model, as evidence that synapsis initiates at sites of recombination events. However, it remains questionable whether all potential initiation sites are actually utilized because detailed comparisons between the number of association sites and the number of short SC stretches have not been carried out. In addition, medium and long SC stretches leave no clues as to their origin, whether from multiple initiations or a low number of initiations combined with SC extension. Also in autotriploids of *Allium* and *Crepis capillaris*, two of the three axial elements of each set of three homologues are synapsed, the third is intimately aligned with and accompanies them throughout their whole length being attached to the SC in a

variable number of sites (Loidl & Jones, 1986; Vincent & Jones, 1993). The persistence of these association sites between SCs and unsynapsed axes in pachytene has suggested that these associations are potential pairing initiation sites, only some of which are realized as SC initiations.

On the other hand, the nucleoproteins of the early nodules are not necessarily active at zygotene. Recent studies in mouse spermatocytes (Plug *et al.*, 1998) have demonstrated changes in protein composition of MNs during zygotene and pachytene, suggesting a differentiation of these nodules during the process of synapsis. These sequential changes indicate that RAD51, a mammalian homologue of *Escherichia coli* RecA protein, is present on both asynapsed and synapsed axes but colocalizes with a single-strand DNA binding protein (RPA) when homologous chromosomes synapse. *In vitro* experiments indicate that RAD51 cannot carry out strand exchange in the absence of RPA. This leads to the conclusion that the activation of RAD51 by RPA occurs at the time of synapsis. If so, these results would suggest a role of SC as a prerequisite for recombination.

Synaptic patterns and chiasma distributions

Both yeast and traditional views of meiosis are able to explain the correlations between the frequency and location of SC initiation sites and crossovers (late MNs and/or chiasmata) that have been observed in materials as diverse as the fungus *Sordaria macrospora* (Zickler *et al.,* 1992) and the males of the grasshopper *Pyrgomorpha conica* (del Cerro *et al.,* 1996).

Let me consider two examples in some detail: (i) Maguire & Riess (1994) observed in maize heterozygous for a short paracentric inversion, a consistent relation in the inverted region between the frequency of homologous synapsis at pachytene, the frequency of late MNs, and the frequency of crossovers estimated from bridge-fragment frequencies at anaphase I and anaphase II. (ii) In the normal monochiasmate S8 bivalents (BB) of the grasshopper *Chorthippus jacobsi*, synapsis usually starts at or near the distal ends of the long arms and the chiasma is preferentially located at these chromosome regions. On the contrary, S8 bivalents heterozygous for a distal supernumerary segment (BS) display a change both in the synaptic pattern and in chiasma distribution. Thus, synapsis is initiated near the pericentromeric region and the single chiasma formed is mainly located there (Santos *et al.*, 1993).

These results concur very well with the idea that recombination is required for synapsis (yeast view). However, Maguire & Riess (1994) do not discard the possibility that crossing over may invariably follow synapsis of the chromosome region involved in the inversion. Another possibility is that inversion loops in which crossover has not occurred are reorganized into nonhomologously synapsed straight regions by dissolution and reassembly of the SC. Also failure of homologous synapsis in the inverted segment at zygotene could lead to nonhomologous synapsis at mid pachytene (Rasmussen & Holm, 1979). On the other hand, chiasma redistribution observed in grasshopper bivalents heterozygous for supernumerary segments of *Ch. jacobsi* males could be explained by the existence of heterosynapsis in the region near the extra segment at late zygotene–early pachytene. The bivalents exhibited SC formation with equalized axial lengths, and absence of chiasmata in those regions in which nonhomologous synapsis took place (Santos *et al.*, 1993). This could also be an adequate explanation for those chiasma redistributions produced by other supernumerary segments in the grasshopper *Stenobothrus festivus* despite in this species there being no differences in the patterns of initiation of synapsis displayed by BB and BS bivalents (del Cerro & Santos, 1997).

The relationship between the patterns of synapsis to distributions of late MNs and chiasmata is not so evident in other species because the number of sites of synaptic initiations do not correspond with the number of late MNs/crossovers, or because synapsis initiates in regions that are devoid of chiasmata. For instance, in plants with long chromosomes the number of synaptic initiations may greatly exceed the number of chiasmata (Hasenkampf, 1984; Gillies, 1985). On the other hand, from the the frequency of pairing partner switches in tetraploid yeast, Loidl (1995) has estimated that stable synapsis is initiated at $\sim$22 sites per diploid nucleus while the mean number of crossovers per nucleus is about 75. In tomato translocation heterozygotes, synapsed arms often lack late MNs (Herickhoff *et al.*, 1993) and in oocytes of *Triturus cristatus* and pollen mother cells of *A. fistulosum* crossovers are localized proximally (near the centromere) and the proximal regions of homologous chromosomes come into contact late, only by zipper-like growth of SC which is initiated distally (e.g. Albini & Jones, 1987). Also telocentric medium-sized bivalents of *St. festivus* show a single chiasma, mostly distally located, and synapsis starts at centromeric regions (del Cerro & Santos, 1997). It is likely that in these cases crossovers form only when the SC has conferred the initial homologous contacts to proximal (*T. cristatus* and *A. fistulosum*) or distal (*St. festivus*) regions.

In contrast with this traditional view, it can be argued that some synaptic initiations are only accompanied by nonreciprocal recombination events. But, what is the magnitude of this phenomenon? Unfortunately, data on gene conversion events in higher eukaryotes are very scarce due to technical difficulties in obtaining them. In the *rosy* locus of *Drosophila*, noncrossovers exceed crossovers by a factor of four (Hilliker & Chovnick, 1981). In yeast and *Neurospora* crossing over was associated in most cases with $\sim$35% of conversion events although gene conversion alone accounts for more than 90% of recombination events at the *am* locus of *Neurospora crassa* (Bowring & Catcheside, 1996).

Achiasmate organisms and recombination-defective mutants

The existence of achiasmate organisms that show complete SC formation such as *Bombyx* females (Rasmussen & Holm, 1979) and the males of a number of species from two families of Australian scorpions (Shanahan & Hayman, 1990) indicates that the SC does not determine the occurrence of crossing over, but is synapsis dependent on nonreciprocal recombination in these organisms? In *Drosophila* for

instance, there are meiotic mutants proficient in gene conversion but deficient in crossing over that assemble SCs normally (Carpenter, 1979). Data from *Bombyx* (Rasmussen & Holm, 1982) indicate that in chiasmate spermatocytes, early MNs appear at early zygotene simultaneously with the initiation of the SC formation and increase in number by late zygotene (about 91 per nucleus). Between late zygotene and early pachytene, the number decreases by 41%. A drastic reduction in the number of MNs could be related to the occurrence of reciprocal and nonreciprocal recombination. In achiasmate oocytes, no MNs of either type were observed, so it seems that in silkworm females synapsis might be independent of recombination.

Two other cases that exemplify a similar situation have been reported recently. (i) Female *Drosophila* homozygous for either of two mutations, *mei W-68* and *mei-P22*, are characterized by an elimination of gene conversion, elimination of crossing over, lack of DSBs and failure to produce early or late MNs, but still develop normal SC (McKim *et al.*, 1998). However, it remains to be ascertained, whether the existence of somatic pairing between homologues somehow conditions the meiotic process in this species. (ii) Dennburg *et al.* (1998) have found in the nematode *Caenorhabditis elegans* that a homologue of the yeast DSB-generating enzyme Spo11p is required for meiotic exchange. The enzyme can be by-passed by radiation-induced breaks, indicating that the initiation of meiotic recombination is conserved in this species. In addition, in a *C. elegans spo-11* null mutant, homologous synapsis occurs normally.

Elimination of multivalents

Rasmussen & Holm (1979) reported a drastic reduction in the number of multivalents between early and late pachytene in achiasmate autotetraploid females of *Bombyx mori* but not in chiasmate autotetraploid males (Rasmussen, 1987). This remarkable sex-dependent difference in the behaviour of multivalents during meiotic prophase was interpreted as the occurrence of crossing over at pachytene in the male preventing further conversion of quadrivalents into bivalents. On the contrary, the absence of crossovers in the female enabled such conversion prior to the SC modifications required to maintain bivalents until metaphase I. The elimination of multivalents is a common process in other polyploid species from genera such as *Triticum*, *Scilla*, *Lotus*, *Lolium* and *Festuca* (Holm, 1986; White *et al.*, 1988; Davies *et al.*, 1990; Jenkins & White, 1990; Thomas & Thomas, 1993). It is proposed that the diploid behaviour displayed by these species is the result of a high pairing stringency of homologous chromosomes at zygotene, which is followed by a correction mechanism that transforms multivalents into homologous bivalents during zygotene and pachytene and, ultimately, by suppression of crossing over in any homoeologous SC segments that might persist at this stage (Martínez *et al.*, 1996 and references therein).

Since the elimination of multivalents would depend on whether or not they are fixed by crossovers, this process has been interpreted as supporting the traditional view that crossing over occurs within the framework of the SC. However, this evidence does not exclude the initiation of recombination events much earlier in prophase I.

Ectopic recombination

Ectopic gene conversion in yeast between artificially induced repeats (two alelles present at the normal locus and another one or several copies inserted elsewhere in the genome) is associated with crossing over of flanking sequences. However, it is not associated with reciprocal recombination when measured between naturally occurring repeats such as Ty retrotransposons (Parket *et al.*, 1995). Therefore, although ectopic gene conversion may be a consequence of genome-wide homology scanning in yeast, mechanisms also seem to exist that suppress ectopic reciprocal recombination, and hence chromosome rearrangements. In fact, a mutant (*hop 2*) described recently shows a phenotype consisting of wild-type amounts of SC, but most chromosomes engaged in synapsis with nonhomologous partners (Leu *et al.*, 1998).

Mechanisms that prevent ectopic recombination seem also to exist in mammals since the analysis of the synaptic behaviour in a mouse hemizygous for two transgenes (*lacI* and *lacZ*) present in chromosomes 4 and 3, respectively, did not reveal the existence of SC formation between the two transgenes (Moens *et al.*, 1997). In addition, similar mutants to *hop2* have been also described in rye (Fedotova *et al.*, 1994). However, the nonavailability of allelic homology in haploid meiosis promotes ectopic reciprocal recombination both in yeast (about 6% of events per meiosis; Loidl & Nairz, 1997) and plants (about 0.38 chiasmata per meiocyte in rye; Santos *et al.*, 1994). The differences between both materials probably being due to the rareness of repeated sequences in yeast compared with higher plants. At least in haploid rye, the correspondence between the location of SC initiation sites and chiasmata indicates that early synapsis could be confined to homologous regions.

Concluding remarks

The available experimental evidence on the relationship between synapsis and recombination does not assist greatly in deciding between the two conflicting views about this subject because many observations can be interpreted to support either of them. The data from yeast suggest that SC formation may require initiation of recombination or, alternatively, that recombination and SC formation are mutually interdependent processes. However, data from *Bombyx*, *Drosophila* and *C. elegans* suggest that, at least in these organisms, SC formation does not require initiation of recombination. Furthermore, in other species the correspondence between SC initiation sites and recombination events is not always evident. A synthetic hypothesis might be that there is a certain variation between organisms in the commitment to recombination and it may occur before, during or just after the initiation of synapsis (Maguire, 1977), but only some kinds of synaptic initiation sites would be resolved as crossing overs which ensure proper chromosome segregation. In higher eukaryotes, a large-scale synapsis could represent a security mechanism to avoid reciprocal exchanges between

homologous DNA sequences at nonhomologous chromosomal regions.

Acknowledgements

I am very grateful to Gareth Jones for many stimulating discussions on the meiotic process. I thank Andrew Pomiankowski and anonymous reviewers for comments of the manuscript and to Spanish colleagues: P. Arana, J. Cabrero, J. P. M. Camacho, N. Cuñado, M. Díez, A. M. Figueiras, C. García de la Vega, M. Martínez, T. Naranjo, C. Romero, J. S. Rufas and J. A. Suja for their useful advise. I apologize to those researchers whose work was not cited due to the brevity of this review. This work was supported by the grant PB95–0421 awarded by the Dirección General de Enseñanza Superior (DGES).

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Note added in proof

A Spo 11 homologue has also been found in the *mei-W68* mutant of *D. melanogaster* (McKim & Hayasi-Hagihara, 1998). On the other hand, the mouse RecA-like gene *Dmc1*, that is specifically expressed in meiosis, seems to be required for homologous chromosome synapsis (Pittman *et al*., 1998; Yoshida *et al*., 1998).

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