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Peculiarities of Meiosis in *Drosophila*: A Classical Object of Genetics Has Nonstandard Meiosis

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Abstract—Meiosis in *Drosophila* differs from the canonical type. Males lack synaptonemal complexes, chiasmata, and crossing-over. Only females have these classical traits of meiosis. However, during meiosis prophase I, female *Drosophila* lack the bouquet-like chromosome arrangement, an accessory mechanism for homologous chromosomes synapsis that is typical for the majority of eukaryotes. Instead, the pericentromeric heterochromatic regions of chromosomes are fused into the chromocenter. This leads to peculiarities in the pairing, synapsis, and segregation of chromosomes and to the so-called interchromosomal phenomena (effects). During late prophase I in females, chromosomes are packed in a karyosome, which is also characteristic of females in other animals with the nutrimental type of egg nutrition. The dissimilarities of meiosis in *Drosophila* from the classical scheme do not affect significantly its genetic consequences.

Keywords: meiosis, synaptonemal complex, crossing over, chromosomes, chromocenter

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INTRODUCTION

Drosophila occupies a special place among the model objects used to study meiosis. Meiosis in *Drosophila* has been studied for a long time and in detail. There are two reasons for this. First, *Drosophila* is the first genetic object (since 1910) and has long been one of the few model objects of genetics. Second, *Drosophila* remains largely unique in terms of cytogenetics, including meiosis cytology. In biology, exceptional cases often make an important contribution to understanding the fundamental mechanisms. This is especially true in the case of meiosis in *Drosophila* (Orr-Weaver, 1995).

Meiosis in *Drosophila* differs from the canonical type in a number of specific features. First, *Drosophila* males lack synaptonemal complexes, genetic recombination, chiasmata, and crossing-over. Second, females lack telomere clustering in a single zone of the nucleus in prophase I and a bouquet-like chromosome arrangement, an important accessory mechanism for homologous chromosome synapsis that is typical for the majority of eukaryotes. Instead, pericentromeric heterochromatic regions of all chromosomes in prophase I are fused into a single chromocenter, which apparently plays the role of telomere clustering but leads to peculiarities in the pairing, synapsis, and segregation of chromosomes and to the so-called interchromosomal phenomena (effects) (Orr-Weaver, 1995). Third, in late prophase I, all chromosomes of *Drosophila* females are packaged in a compact karyosome; however, this is also characteristic of females of other animals with the nutrimental type of egg nutrition (Gruzova et al., 1972; Gruzova, 1975; Orr-Weaver, 1995). Fourth, the small fourth chromosome does not undergo crossing-over and does not form chiasmata but segregates successfully (Baker and Hall, 1976). It is assumed that the dense chromosome packing in the karyosome maintains the association of homologs even in nonexchanged (non-crossover) bivalents (Orr-Weaver, 1995). Hawley et al. (1993) showed that the proper segregation of achiasmate chromosomes requires heterochromatic homology. In some cases, heterologous chromosomes may also segregate, though by another mechanism (see. section Chromocenter). As a result, meiosis in *Drosophila* females proceeds with characteristic morphological differences from the classical scheme; this, however, does not affect significantly its genetic consequences.

GENERAL MORPHOLOGY OF GONADS IN *Drosophila*

Morphology of Gonads in Females. Oogenesis

Drosophila ovaries are paired formations located in the middle of the abdomen. In mature flies, the ovary size reaches 100 μm. Each ovary consists of 10–30 parallel egg tubes (ovarioles). Each ovariole is divided into the germarium and vitellarium.

The uppermost part of the germarium (Fig. 1, region 1) contains a stem cell that periodically divides

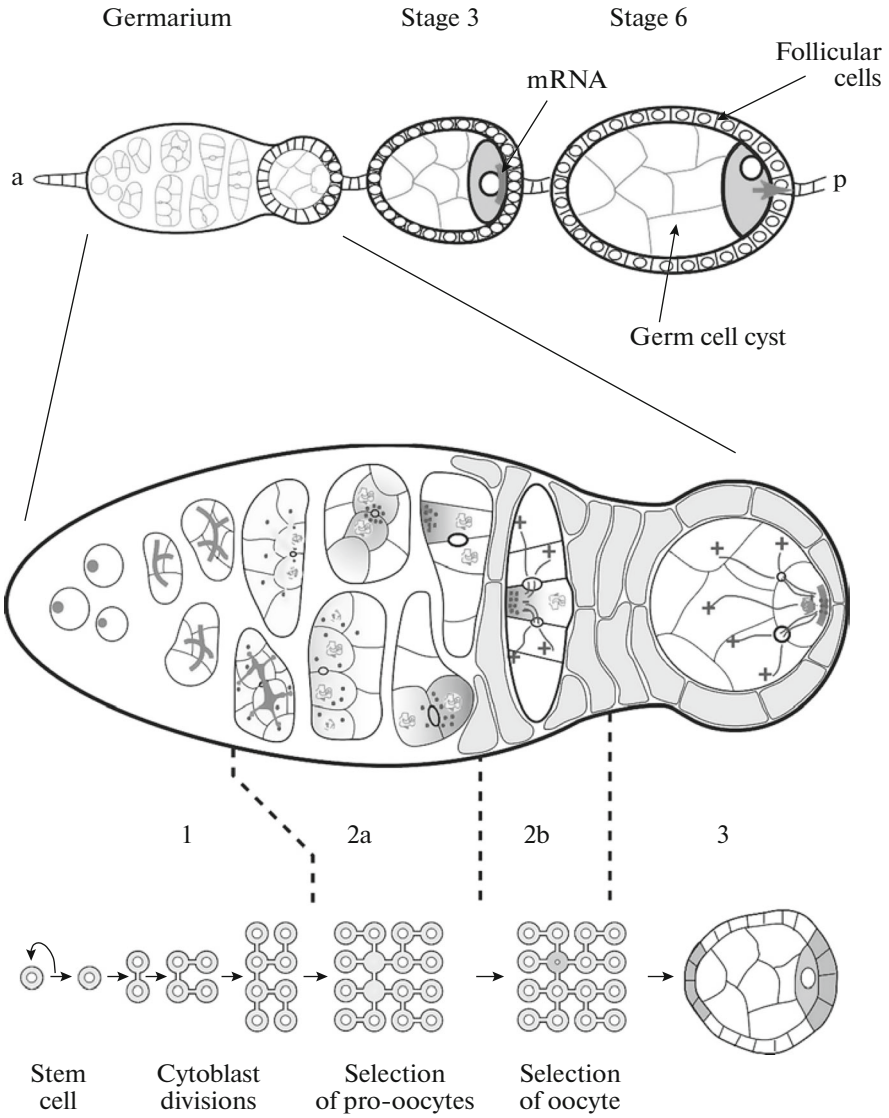

Fig. 1. Early oogenesis in *Drosophila* (by Huynh and Johnson, 2004, with modifications). The germarium and the first egg chambers (top row), a close view of the germarium with specified regions (middle row), and the scheme of the formation of a 16-celled cluster (bottom row) are shown. Designations: a (anterior)—anterior part of the ovariole, p (posterior)—posterior part of the ovariole.

into two unconnected cells, one of which remains a stem cell and the other forms a 16-cell cluster as a result of successive mitoses. This takes place in the germarium.

All cells of the 16-celled cluster (cystocytes) are interconnected by 15 properly distributed circular channels such that two cystocytes have four channels, two have three channels, four have two channels, and eight have one channel (Fig 1, below). Two cells with four circular channels differ from other cluster cells by the nuclear differentiation type (they both enter the meiosis prophase in region 2 of the germarium) (Cahoon and Hawley, 2013). These cells are called pro-oocytes (Fig. 1, upper part, region 2a), and the remaining cells are the progenitors of nurse cells.

Further development of pro-oocytes proceeds in the vitellarium. The vitellarium comprises four to nine linearly arranged egg chambers (King, 1970a, 1970b; Litvinova, 1977; Spradling, 1993).

At the electron-microscopic level, oocytes are characterized by the presence of synaptonemal complexes (SCs) (King, 1970a, 1970b; Egel, 1978; Buning, 1994; McKim et al., 2002). Later, SCs also develop to different degrees in other cells of the cluster with a smaller number of circular channels, where meiosis proceeds to the zygotene stage (Carpenter, 1975a, 1994; Liu et al., 2002). Moreover, the molecular components of SCs in the pericentromeric region were identified even in mitotically dividing cells in region 1 of the germarium (Christophorou et al., 2013). It was shown that such centromeric pairing during mitosis

facilitates the clustering of centromeres during meiosis (for details, see below).

Germ cells actively divide in the gonads of young larvae (Litvinova, 1977). The formation of cystocytes and their differentiation into two types of cells begin in pupas and continue in adult flies. All of these processes take place in the upper third of the germarium. The cluster then begins to move downwards in the germarium, acquiring a layer of follicular cells (King, 1970a, 1970b; Egel, 1978; McKim et al., 2002). There are 4–11 16-cellular clusters in the germarium. They are arranged in a certain order, though nonlinearly (Carpenter, 1975a; McKim et al., 2002).

Upon the transition from the germarium to the vitellarium (Fig. 1, region 2b), the SC in the nucleus of one of the pro-oocytes gradually disappears. Thus, meiosis in this cell is not completed, and it becomes a nurse cell. Only one oocyte continues to develop (Fig. 1, region 3), and meiosis proceeds only in it. The selection of the oocyte from the two pro-oocytes is determined by the formation of a certain asymmetry during the first division of the cytoblast, and this asymmetry is maintained until oocyte differentiation (Huynh and Johnson, 2004). Since that time, the oocyte is located in the lower part of the cluster, and the cluster acquires a spherical shape (Rasmussen, 1974; Huynh and Johnson, 2004). At this time, the mitochondria, centrosome, Golgi vesicles, marker proteins (BicD, Orb, Btz, and Cup), and mRNAs (*osk*, *BicD*, and *orb*) form a typical Balbiani body in the frontal part of the oocyte. It was shown earlier that the pro-oocyte that has a larger contact area with the follicular cells becomes the oocyte (Koch et al., 1967).

The vitellarium is divided into the egg chambers. They pass a series of successive stages (S_1 in the germarium and S_2–S_{14} in the vitellarium), ending with stage S_{14} (mature primary oocyte). At stages S_1–S_6, all 16 cells of the cluster grow at the same rate. The oocyte then grows much faster than the nurse cells, which gradually degenerate (King, 1970a, 1970b). The chromosomes begin to condense at stage S_3 and aggregate into a compact karyosome. At stage S_{13}, when the nuclear envelope disappears, the karyosome enters the ooplasm and is now called the karyosphere (King, 1970a, 1970b). The mature egg ceases to develop at metaphase stage I (Litvinova, 1977).

Structure of Gonads in Male Drosophila. Spermatogenesis

The testes of *Drosophila* are helically coiled tubes approximately 2 mm in length and approximately 100 μm in diameter. In the testis duct, the upper part is occupied by the primary germ cells, followed by spermatocyte clusters, which occupy approximately 1/3 of the tube length. The rest part of the testes is occupied by bundles of elongated spermatids (Litvinova, 1977).

Each secondary spermatogonium yields 16 primary spermatocytes (PSs), of which 64 spermatids are formed as a result of two meiotic divisions. All PS cluster cells form a syncytium and are connected by circular channels. The distribution of channels in cells is presumably the same as in females. The cluster cells develop synchronously (Rasmussen, 1973).

BEGINNING OF MEIOSIS: INITIATION OF PAIRING OF HOMOLOGOUS CHROMOSOMES

In meiosis, the initiation of pairing of homologous chromosomes in the majority of eukaryotes begins after the formation of DNA double-strand breaks (DSBs). They are produced by endonuclease SPO11 (Page and Hawley, 2003). However, in some organisms (including the nematode *Caenorhabditis elegans* and *Drosophila*), homologous pairing proceeds normally in the absence of DSBs. Such pairing may be provided either by the premeiotic pairing maintenance mechanism or by the pairing of homologous chromosomes based on the aggregation of proteins that specifically bind to DNA. It was believed for a long time that meiotic pairing in *Drosophila* is preceded by mitotic pairing, facilitating it in the absence of DSBs. However, recent studies have shown that the processes are quite different (Cahoon and Hawley, 2013). First, homologous chromosomes are not paired in the germline stem cells. Their pairing begins in five mitotic divisions before meiosis (Joyce et al., 2013). Second, proteins of synaptonemal complexes associated with the pericentromeric chromosomal regions were found in these cells (in a four-cell cyst) (Christophorou et al., 2013). Thus, the meiotic pairing of chromosomes in *Drosophila* begins much earlier than previously believed, namely, during the mitotic divisions preceding meiosis. It was established that some proteins of the SC—Cona and C(3)G—are located in region 1 of the germarium (Fig. 1), in the cells that divide by mitosis (Christophorou et al., 2013), and cause the pairing of the centromeric chromosomal regions. It is unclear how in this case the sister chromatids can segregate without errors. It was assumed that this oogonial "centromeric SC" differs from the true meiotic SC, which is characteristic of the entire oocyte chromosome length.

It was recently shown that the initiation of homologous chromosome synapsis includes three stages (Tanneti et al., 2011). In oocytes in the early zygotene, synapsis occurs only in the centromeric region. In oocytes in the middle zygotene, SC begins to form in several euchromatic sites; this process depends on the cohesin protein ORD. In the late zygotene, SCs are formed in numerous sites, and this process requires the protein C(2)M. Events in the late zygotene do not depend on the events in the middle zygotene, although both stages require cohesins SMC1 and SMC3. The authors hypothesized that the concentration of

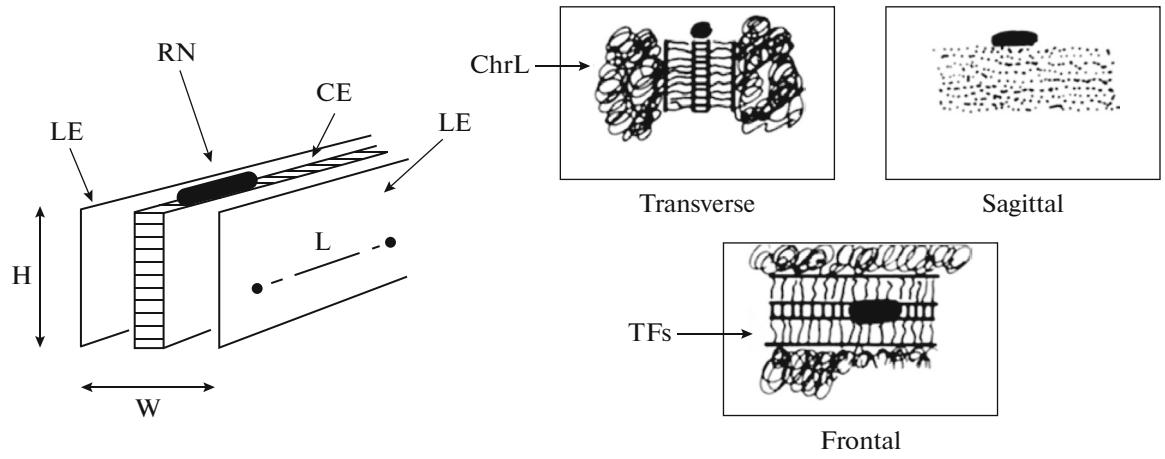

Fig. 2. Scheme of the structure of the synaptonemal complex (SC) of *Drosophila* (by Carpenter, 1979, with modifications). A 3D image of the SC and sections in three planes are shown. Designations: LE—lateral SC elements, CE—central element, RN—recombination nodule, ChrL—chromatin loops, H—conventional SC height, W—SC width, L—SC lenght, TFs—transverse filaments.

cohesin proteins in specific sites is required to initiate the pairing of homologous chromosomes in the absence of DSBs.

SYNAPTONEMAL COMPLEXES IN *Drosophila* FEMALES

Synaptonemal Complex Morphology

The synaptonemal complex in *Drosophila* females has the typical structure (Carpenter, 1975a, 1979). This is a three-part rod-like structure consisting of two lateral elements (each approximately 17 nm wide) and a central space between them that is 100–120 nm wide. A well-structured longitudinal central element is located in the middle of the central space (Fig. 2).

SC formation in *Drosophila* differs from that in other organisms. Axial bands (unpaired lateral elements (LEs)) in the leptotene are not detected (Rasmussen, 1974). SC formation begins in the zygotene, which proceeds in the germarium, and the fully formed SC is detected in the pachytene, which also begins in the germarium (Carpenter, 1975a). A complete or partial absence of synapsis is sometimes observed in the whole arm of the chromosome in *Drosophila*, and the SC in the distal part of the X chromosome is often discontinuous (Carpenter, 1979). The telomeric ends of bivalents are attached to the nuclear membrane. However, there is no connecting plate between the telomere and the nuclear membrane, which is typical for other species. SC undergoes disintegration in the diplotene, and only its amorphous fragments remain. In light of studies on other organisms, these remains of the SC should be located in the chiasmata (Rasmussen and Holm, 1980; Bostock and Sumner, 1981; Zickler and Kleckner, 1999).

In meiosis prophase I in *Drosophila*, chromosomes are joined in the chromocenter. This nuclear organization is reflected in the presence of two morphological types of SCs (euchromatic and heterochromatic). The euchromatic SC has a distinct lattice-like central element 28–32 nm wide, which is connected with the amorphous lateral elements by thin transverse filaments (Carpenter, 1975a). The SC height varies both within the cell and between cells from 75 to 210 nm. Chromatin does not surround the entire SC and is located at the side of the lateral elements (Fig. 2). The euchromatic SC is semirigid and can rotate around the axis of the central element and bend in the sagittal (vertical) plane. In the frontal (horizontal) plane, the possibility of bending is much lower (Carpenter, 1975a).

The heterochromatic SC has a much less distinct structure. The central element is amorphous, and the lateral elements are often indistinguishable from chromatin. The width of the central region is the same as that of the euchromatic SC, and the height is 30–75 nm. Chromatin is more condensed and surrounds the entire SC. This SC is more flexible than the euchromatic one. The SC becomes higher and more clearly structured as the distance from the centromere increases. The heterochromatic SC passes into the euchromatic one without break (Carpenter and Baker, 1974).

Synaptonemal Complex Proteins

It is known that, although the general morphology of the SC is retained in different evolutionary branches of eukaryotes (fungi, plants, and animals), the proteins forming this structure are considerably different (Penkina et al., 2002; Anuradha and Muniyappa, 2005; Grishaeva and Bogdanov, 2014). The same function of the proteins constituting the SC is not associated with the homology of their primary structure. In this respect, *Drosophila* is a unique object, because the proteins that form its SCs do not have

orthologs in other organisms (Page et al., 2008; McKim et al., 2002; Grishaeva and Bogdanov, 2014).

In *Drosophila*, chromosome synapsis in meiosis forms under the control of the *c(3)G* gene (Smith and King, 1968), which was discovered as early as 1922. In 2001, it was established that the protein encoded by this gene forms the transverse filaments of SC in *Drosophila* (Grishaeva et al., 2001; Page and Hawley, 2001). This protein is encoded by the *c(3)G*, *crossover suppressor on 3 of Gowen* gene (genetic coordinates: 3–58 (chromosome 3); cytological coordinates on Bridges map: 89A5, disk 89, section A5) (FlyBase). This 744-aa protein has an extended region with an alpha-helical structure in the central part of the molecule. This structure allows two parallel molecules of the C(3)G protein to form a rod-like dimer, and two oppositely directed dimers form the SC transverse filament (Roeder, 1997). The C(3)G protein is similar in size, domain organization, and secondary structure to SYCP1, Zip1, and ZYP1 proteins, which perform a similar function in metazoans, fungi, and plants, respectively (Grishaeva et al., 2001; Bogdanov et al., 2002). This protein contains two bacterial SMC (structural maintenance of chromosomes) domains that are found in many structural chromosomal proteins (Grishaeva and Bogdanov, 2014). The slightly peculiar physicochemical properties do not affect the implementation of the required function by this protein, which we showed when simulating the interaction of two C(3)G molecules (Bogdanov et al., 2007).

The SC of *Drosophila* also comprises the C(2)M protein (Manheim and McKim, 2003). This protein is encoded by the *c(2)M* gene, *crossover suppressor on 2 of Manheim* (2–52; 35F1) (FlyBase). Although the C(2)M protein is distantly related to the kleisins of other organisms, including the meiosis-specific cohesin REC8, it is apparently not involved in the sister chromatid cohesion and performs functions within SC (Heidmann et al., 2004). This 570-aa protein contains cohesin domains RAD21 and REC8 (Grishaeva and Bogdanov, 2014). It is possible that it is not a component of SC lateral elements but rather connects the C(3)G protein with them (Fig. 3) (Anderson et al., 2005; Hawley, 2011). This protein has no alpha-helical regions (Grishaeva, unpublished data).

Another candidate protein of SC lateral elements in *Drosophila*, ORD, was discovered a long time ago (Bickel et al., 1996); however, the discussion of its possible role in the SC structure began later (Hawley, 2011). It was known earlier that mutations in the gene encoding this protein disrupt the cohesion of sister chromatids and cause their premature disjunction in meiosis, as well as a decrease in the crossover frequency (Grishaeva and Bogdanov, 2000). The ORD protein is 479 aa long and comprises a small ribonucleotide diphosphate reductase domain. In addition, a short segment with the alpha-helical configuration is present in the central part of this protein (our data).

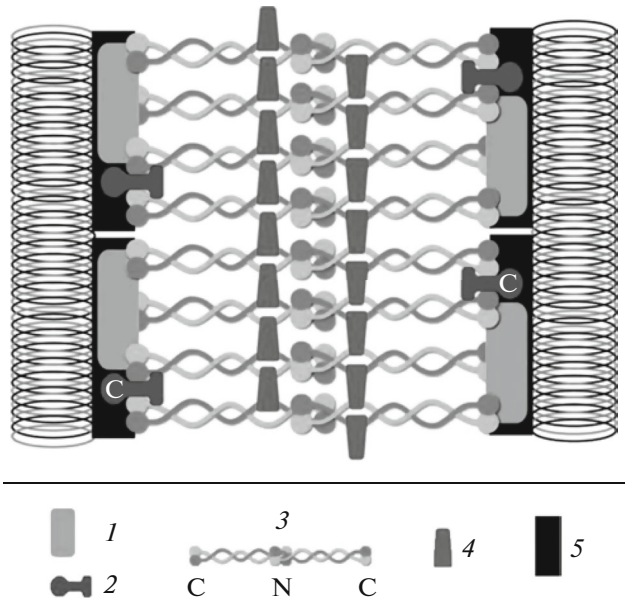

Fig. 3. Structure of the synaptonemal complex of *Drosophila* (by Hawley, 2011, with modifications). Designations: *1*—ORD protein; *2*—C(2)M protein; *3*—two dimers of the C(3)G protein arranged in tandem (each protein is composed of molecules arranged in parallel with long alpha helices); *4*—Cona protein, which forms pillars; *5*—proteins of SC lateral elements. Letters N and C designate the N- and C-terminal globular domains of the C(3)G protein.

This protein is encoded by the *ord* gene (2–102; 59D4) (FlyBase).

The fourth known SC protein of *Drosophila* is CORONA (CONA) (Page et al., 2008). This small 207-aa protein stabilizes the transverse SC filaments consisting of C(3)G dimers (Fig. 3) and is a classical "pillar" that supports several transverse filaments (Hawley, 2011). This protein contains no alpha-helical regions and has no functional domains. It is encoded by the *corona* gene (3–63; 91A5) (FlyBase).

A fifth SC protein of *Drosophila*, Corolla, was recently discovered (Collins et al., 2014). It is a component of the central SC region (and, possibly, even a component of the transverse SC filaments) and interacts with the CONA protein. It is 554 aa long and contains three alpha-helical segments. This protein also comprises the CDK-activating kinase assembly factor MAT1 domain (Grishaeva, unpublished data). This protein is encoded by the *corolla* gene (1–57, 16B10) (FlyBase). The Corolla protein has three short regions of homology with the SYP-4 protein of *C. elegans*, a component of the SC of this nematode, and is, possibly, an ortholog of the latter (Collins et al., 2014). This is the only similarity of the SC proteins of *Drosophila* with the proteins of other eukaryotes that have the same structural functions in their SCs. The place of the Corolla protein in the molecular structure of the SC of *Drosophila* remains obscure. It is not shown in Fig. 3, and this schematic representation of the molec-

ular organization of the SC of *Drosophila* may be changed in the near future.

CROSSING-OVER, RECOMBINATION NODULES, AND CHIASMATA

As mentioned earlier, SC formation in *Drosophila* does not depend on the appearance of DNA DSBs. However, the opposite dependence is observed: the SC is required for the appearance and repair of DNA DSBs. The MEI-P22 protein, which is not an ortholog of SPO11 (the MEI-W68 is an ortholog), does not have analogs in other organisms. However, in *D. melanogaster*, it is required for the formation of DNA DSBs. The MEI-P22 protein lands on the sites that will be the future sites of DNA breaks (McKim et al., 2002). The foci of this protein appear for a short time in the early prophase I of meiosis at stage 2a of germarium development (Fig. 1). The foci of phosphorylated histone γH2AX, which is a marker of DNA DSBs, appear on chromosomes after the completion of SC formation. The number of DNA DSBs in *Drosophila* females is apparently regulated by the restricted access of the MEI-P22 protein to chromosomes. The aforementioned changes in SC morphology in pachytene (its shortening and thickening) may contribute to this (Carpenter, 1975a). In total, up to 24 DNA DSBs per cell form in *Drosophila* (Jang et al., 2003; Lake and Hawley, 2012). The MEI-P22 protein is encoded by the *mei-P22* gene (3–19, 65E9) (FlyBase).

The SC is also required for the successful completion of crossing-over (Heiting, 1996; Page and Hawley, 2004). In particular, it is believed that the involvement of SC in the molecular mechanism of crossing-over in *Drosophila* is associated with the activity of the C(2)M protein, an SC component (McKim et al., 2002). This differentiates *Drosophila* from other model species, e.g., from the yeast *S. cerevisiae*, in which the crossing-over frequency in the absence of SC in the *zip1* mutants does not tend to zero but is reduced only by half.

The markers of recombination sites on chromosomes are the so-called recombination nodules (RNs)—electron-dense structures associated with SC (Fig. 2) that consist of a complex of proteins involved in recombination (Penkina et al., 2002; Basheva et al., 2008). RNs are present in the pachytene in all organisms that undergo recombination (Carpenter, 1979). In *Drosophila*, two morphological types of RNs—spherical and ellipsoidal—were found (Carpenter, 1975b). Two RN types were also found in the green alga *Chlamydomonas*, fungus *Neurospora*, and many other organisms (Zickler and Kleckner, 1999). They differ in size, number per nucleus, distribution along bivalent arms, time of appearance, and protein composition in them. The ellipsoidal RNs appear and disappear earlier. They are distributed more or less homogeneously along the chromosome arms, and their number is greater than the number of the spherical RNs. The distribution of the spherical RNs coincides with the distribution of crossover events. Like chiasmata, they exhibit interference, which is not observed for the ellipsoidal RNs. The ellipsoidal RNs may mark the gene conversion (nonreciprocal exchange) sites (Carpenter, 1979). DNA is synthesized in both RN types, which confirms their involvement in the genetic recombination events (Carpenter, 1981).

The only structural component of RNs identified in *Drosophila* is the 237-aa protein Vilya, which is encoded by the *vilya* gene (coordinates 1–1.5, 3B3) (FlyBase). It belongs to the RING Finger family proteins and contains the zinc-RING finger domain and the coiled-coil domain characteristic of the proteins associated with the polar body of the spindle. This protein is homologous to Zip3-like proteins, which determine the fate of DSBs in other organisms. In *Drosophila*, it marks the sites of crossing-over (Lake et al., 2015).

The complex of proteins that form RNs has been studied quite comprehensively in yeast and mammals (Ross-Macdonald and Roeder, 1994; Hollingsworth et al., 1995; Hunter and Borts, 1997; Chua and Roeder, 1998; Moens et al., 2001; Basheva et al., 2008). Due to the conservation of the molecular bases (mechanisms) of meiosis, this notion is also extrapolated to *Drosophila*. However, there is no doubt that RN proteins will also be studied in *Drosophila*, which may broaden the notion of the variability of important specific meiotic proteins.

The complex of proteins that are RN components changes during prophase. It includes recombination enzymes and structural proteins. Studies in yeast *S. cerevisiae* showed that SPO11 (endonuclease) produces double-strand breaks in DNA. Early RNs then appear. They contain the Rad50/Mre11/Xrs2 protein complex, which is required for the processing of single-strand DNA ends in DSB sites (Chua and Roeder, 1998). DMC1 (meiotic homolog of RAD21) directs the 3' ends to the chromatid of another homolog, and RAD51 interacts with the proteins that cause 5'-end degradation. RPA and RAD52 then displace RAD51/DMC1 from RNs, and the BLM protein lands there (Moens et al., 2001). The late RNs comprise MLH1, an enzyme that replaces the incorrectly inserted nucleotides, which was shown for mammals (Basheva et al., 2008) and yeast (Hunter and Borts, 1997). In yeast, RNs also comprise enzymes Msh4 and Msh5 (Ross-Macdonald and Roeder, 1994; Hollingsworth et al., 1995).

An important issue is the distribution of crossing-over events (and chiasmata) along chromosome arms. In *Drosophila*, meiotic abnormalities at all stages of meiotic recombination preceding the Holliday structure resolution affect the distribution of exchange events along chromosomes (McKim et al., 2002). This is important because the distal chiasmata may not properly retain chromosomes in metaphase I, and it is difficult to resolve the proximal (close to the centromere) chiasmata, because this process is not the

result of their terminalization but is instead due to the loss of contact (cohesion) of sister chromatids. According to statistics, the proportion is slightly more than one crossover event (and, therefore, one chiasmata) per arm of a large *Drosophila* chromosome, and it is likely that an exchange will take place in the middle of the arm (Baker and Hall, 1976; Hawley et al., 1993). Crossing-over is suppressed near the centromere, which may be explained by the presence of a heterochromatic chromocenter (Novitski, 1975). Heterochromatin always inhibits crossing-over in adjacent loci (Prokof'eva-Bel'govskaya, 1986; Lima-de Faria, 1983).

The effect of various chromosomal rearrangements on the frequency and location of crossing-over events in *Drosophila* is of interest. For example, heterozygous inversions hamper pairing and crossing-over in inverted regions but increase crossover frequency in the noninverted regions (Grell, 1962). In addition, heterozygous inversions affect crossing-over in other chromosomes (the so-called interchromosomal effect) (Lucchesi and Suzuki, 1968; Lucchesi, 1976). The same effect is exerted by heterozygous translocations, as well as compounds XY and XX (Suzuki, 1963). Studies of heterochromatin rearrangements showed that it is also involved in the regulation of recombination. It was found that heterochromatin deletions suppress crossing-over, not only in the given chromosome but also in other, intact chromosomes (Yamomoto, 1979).

Chromocenter

The studying of chromosomal behavior during meiosis in *Drosophila* females revealed a number of features that indicate the absence of independent behavior of nonhomologous chromosomes. This applies not only to the coorientation of chromosomes during the first meiotic division but also to the crossover frequency in the entire *Drosophila* genome (Hawley et al., 1993). The unusual meiotic genetic phenomena in *Drosophila* include the rarely observed chromosomal nondisjunction (Carpenter, 1973), the nonrandom distribution of nonhomologous chromosomes (Oksala, 1962), and the interchromosomal effect on chromosome nondisjunction and crossing-over (Cooper et al., 1955). Disturbed pairing in at least one pair of homologs or the presence of supernumerary chromosomes (univalents) led to chromosomal nondisjunction, nonhomolog coorientation in metaphase I, and an increased crossover frequency in normally paired regions and whole chromosomes. The absence of exchanges in chromosomes at their primary or secondary nondisjunction was also observed (Grell, 1962).

Many researchers explained the interchromosomal effects by the presence of the chromocenter, which combines all centromeric regions of chromosomes in *Drosophila* as a whole (Dävring and Sunner, 1973; Nokkala and Puro, 1976; Novitski and Puro, 1978; Prokof'eva-Bel'govskaya, 1986). The chromocenter is an intranuclear structure that formed as a result of the association of pericentromeric heterochromatic regions of all or some of the groups of chromosomes. A single chromocenter is not formed in all nuclei. Approximately 25 and 5% of oocytes have two and three chromocenters, respectively (Carpenter, 1979). This structure is observed in the interphase and prophase I of meiosis in the majority of species of *Drosophila*, yeast, plants, amphibians, mammals, and insects (Monakhova, 1973; Prokof'eva-Bel'govskaya, 1986; Funabiki et al., 1993; etc.).

In addition to the meiotic pairing of homologs, mitotic or somatic pairing of homologous chromosomes is observed in many insects (particularly, dipterans) (Kaufman, 1934; Prokof'eva-Bel'govskaya, 1986). The association of pericentromeric heterochromatic regions was also detected in the interphase and prophase of nerve ganglion cells of *Drosophila* larvae (Halfer and Barigozzi, 1973; Prokof'eva-Bel'govskaya, 1986). During mitosis, the chromocenter exists until metaphase, and the centromeric regions of nonhomologous chromosomes are connected by the chromatin filaments (Semenov and Smirnov, 1979). Giant polytene chromosomes of *Drosophila* salivary glands are also fused in the chromocenter (Painter, 1933 (cited by: Prokof'eva-Bel'govskaya, 1986)).

Studies by Chubykin (1995, 2001, 2009) made it possible to understand in detail chromocenter formation in prophase I of meiosis in *Drosophila*. The chromocenter structure is determined genetically. Two groups of chromosomes associated in the pericentromeric regions form in the G_2 phase of the premeiotic cell cycle; all chromosomes are later combined in the chromocenter. They are arranged in the following order: X–2L–2R–3L–3R-4 (Fig. 4). In meiosis, the chromocenter has a two-ringed structure formed by connections of a heteroectopic nature that form between nonhomologs in asynaptic pericentromeric regions of bivalents. Stepwise synapsis of homologs in prophase I of meiosis is initiated prior to or simultaneously with the chromocenter formation. The synapsis of euchromatic regions is followed by the second stage—the pairing of heterochromatin. The formed chromocenter is detected at stages S_3–S_4 of oocyte development. Connections codirecting homologous chromosomes to different poles of the first meiotic division form in the pericentromeric region (Fig. 4a). Disturbance of these connections (e.g., due to structural or locus mutations) is compensated for by the presence of chiasmata between homologs in the pericentromeric region or by the chromocentral connections between nonhomologs, which are retained until prometaphase. In the last case, an "interchromosomal effect" on the disjunction of chromosomes is observed (nonhomologs do not undergo disjunction independently).

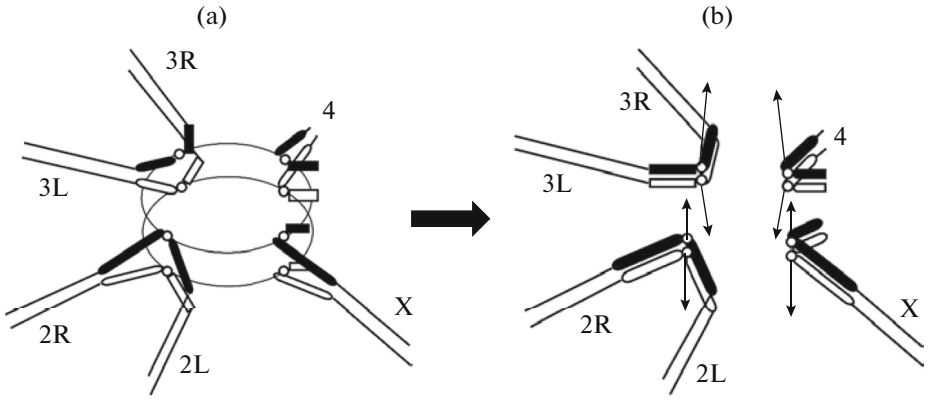

Fig. 4. Scheme of reorganization of the chromocenter in prometaphase I (karyosome) of meiosis in females. (a) Double ring of the chromocenter creates the conditions for the coorientation of homologs in the absence of the pericentromeric synapsis. (b) Replacement of the chromocentral connections with the homologous ones in the pericentromeric heterochromatin regions. The arrows indicate the direction of movement of chromosomes in anaphase I (by Chubykin, 2009, with modifications).

In prometaphase I of meiosis, one of the kinetochores in the bivalent is activated, and stable spindle fibers are attached to it (Fig. 4b). This is accompanied by the degradation of chromocentral connections between nonhomologs and the coordinating connections between homologs. The homologous chromosomes then move apart towards the opposite poles.

In contrast to meiosis, the chromocenter formation in mitotic cells begins in the interface and ends in the prophase of mitosis. A characteristic chromocenter feature is the absence of connections between the pericentromeric regions of homologs, their desynapsis, and the degradation of connections between nonhomologs before spindle formation and stabilization. These conditions are necessary to activate all kinetochores of sister chromatids (Chubykin, 1995, 2001, 2009).

PECULIARITIES OF MEIOTIC DIVISIONS IN *Drosophila*

Peculiarities of Meiotic Divisions in Oogenesis

A common feature of meiosis in females in some organisms is the absence of centrosomes and centrioles, although a bipolar spindle is formed in this case. In *Drosophila*, γ-tubulin, which is a centrosomal component, does not concentrate at the spindle poles but is required for meiosis. The spindle formation in metaphase I begins with the formation of microtubules that "grow" from the chromosomes towards the poles rather than from the poles themselves. Each chromosome forms its own bipolar minispindle (McKim et al., 2002). Spindle formation requires the presence of NCD, NOD, SUB, MSPS, D-TACC, and ASP proteins.

The NOD protein (666 aa long) is encoded by the *nod* (*no distributive disjunction*) gene (also known as *Kif 22*; coordinates 1–36; 10C7–8). Its partner, NCD protein (700 aa long), is encoded by the *ncd* (*non-claret disjunctional*) gene, formerly known as *ca*nd ((*claret nondisjunctional*); coordinates 3–99; 99C1) (FlyBase). Both proteins belong to the kinesin heavy chain superfamily (kinesins are involved in the transport of organelles, protein complexes, mRNA, and motion of the spindle and chromosomes (FlyBase)). The SUB protein (628 aa long) is encoded by the *sub* (*subito*) gene, formerly known as *Dub* (*Double or nothin*g (Moore et al., 1994)); coordinates 2–84; 54E7 (FlyBase). The protein that is a homolog of kinesin-6 binds to the antiparallel microtubules. MSPS has several isoforms 2042 to 2082 aa long and is encoded by the *msps* (*mini spindles*) gene (coordinates 3–58; 89B1–2). This protein binds to microtubular tubulin through several functional domains (HEAT, TOG, etc.). Another spindle component, D-TACC, is the product of the *Dmel\tacc* (*transforming acidic coiled-coil protein*) gene (3–47; 82D2). It has 13 isoforms and varies in length from 245 to 1322 aa. It binds to the spindle microtubules (FlyBase). Lastly, the ASP protein (1954 aa long) is the product of the *asp* (*abnormal spindle*) gene (3–85; 96A19–20). It binds to the myosin light chain (FlyBase).

Before fertilization, the *Drosophila* egg "freezes" (is "arrested" at the metaphase I stage). This moment is a checkpoint of meiosis. If chiasmata between homologous chromosomes are absent, oocytes prematurely enter anaphase I and pass both meiotic division at stage S_{14} (McKim et al., 2002). The escape of the oocyte from metaphase I and its transition to anaphase I normally requires specific proteins. One of the key proteins is Ca(2+)/Calmodulin-dependent phosphatase calcineurin. Its activation and anaphase completion requires the Sarah protein, which, in turn, should be phosphorylated by Shaggy/GSK-3β (glycogen synthase kinase) (Takeo et al., 2012).

Let us briefly discuss these proteins. Calcineurin consists of two components (A and B). The former exhibits catalytic activity (metal-dependent phospha-

tase), and the latter ensures the sensitivity to calcium. Calcineurin A1 has three isoforms ranging in length from 596 to 622 aa and is encoded by the *Calcineurin A1* gene (3–102; 100B1). There is also the calcineurin A1 protein on 14F, its gene is located in section 14E3–14F1 of the first chromosome (genetic coordinates 1–54). The size of this protein is 584 aa. Calcineurin B is a small protein 170 aa long and has a calcium-binding site; its gene is located on the first chromosome (1–11; 4F5). Lastly, the calcineurin B2 protein, which is identical in length and properties to the previous one, is encoded by the gene located on the second chromosome (2–57; 43E16). Calcineurin activator, the Sarah protein (292 aa long) contains an RNA-recognizing domain and is encoded by the *sarah* gene (3–58; 89B7–89B12). The Sarah protein is phosphorylated by the Shaggy/GSK-3β glycogen synthase kinase. The protein is encoded by the *shaggy* gene (1–1; 3A8–3B1) and has approximately 20 isoforms ranging in size from 416 to 1168 aa (FlyBase).

Meiosis in Drosophila Males

A characteristic feature of meiosis in *Drosophila* males is the absence of synaptonemal complexes and crossing-over (Meyer et al., 1961; Rasmussen, 1973); this determines a certain "simplification" of meiosis, which performs only the segregation function (Carotti, 1973).

Drosophila females have specific mechanisms for the segregation of nonexchange (achiasmatic) chromosomes: one is based on the homology of heterochromatic regions, and the other is based on chromosome similarity in size and shape (Hawley et al., 1992). However, the mechanisms involved in meiosis in females are not involved in meiosis in *Drosophila melanogaster* males. Mutations in the genes affecting the disjunction of nonexchange chromosomes in females usually do not affect the segregation of chromosomes in males.

Cytological studies of meiosis in *Drosophila* males showed that the homologous chromosomes are paired at stages from prometaphase I to the beginning of anaphase I (Vazquez et al., 2002). Autosomes are arranged in parallel, whereas the sex chromosomes contact at discrete sites. It is even possible that the homologous chromosomes are paired at stage G_1 and remain paired during the S phase. In young spermatocytes (stages G_1–G_2), numerous contacts of heterochromatic regions of nonhomologous chromosomes (chromocenters) were also observed (Vazquez et al., 2002).

Back in 1964, Cooper (1964), who studied the behavior of sex chromosomes in prophase I of meiosis in *Drosophila* males, discovered certain consistent patterns in this process. For example, the Y chromosome always conjugated with the heterochromatic part of the X chromosome but never with its euchromatic part. In turn, regions of the heterochromatic part of the X chromosome conjugated with both the short (more often) and long arms of the Y chromosome. The length of the conjugation sites was always very small. Cooper proposed the term "collochores" for such sites of sex chromosomes. It was later shown that the pairing sites of X and Y chromosomes are located within rDNA repeats (McKee et al., 1992).

More recent studies clarified the sequence of events during meiosis in *Drosophila* males (Fig. 5). The euchromatic regions of homologous chromosomes are paired in spermatogonia and in the early stages of development of spermatocytes. An intensive segregation of homologs and sister chromatids along the chromosome arms then takes place. It is observed in the middle stage G_2, several hours before the first meiotic division (Vazquez et al., 2002). The centromeres of homologous chromosomes pair specifically in the middle of stage G_2. However, at the end of this stage, they lose contact (the centromeres of sister chromatids remain in a close association). Thus, the interaction of euchromatic regions of autosomes in spermatocytes is required to initiate, but not maintain, meiotic pairing in *Drosophila* males. The study authors assumed that the involvement of heterochromatic regions or tangles of chromatids are required to maintain the association of homologs in the late G_2 phase. It is also possible that the formation of chromosome territories in the spermatocyte nucleus may play an active role in ensuring meiotic pairing specificity in the late prophase I of meiosis by breaking the interaction between the nonhomologous chromosomes (Vazquez et al., 2002).

Regardless of the type of associations of homologous chromosomes in *Drosophila* males, they are sufficient to balance the forces pulling the chromosomes towards the poles in anaphase of the first meiotic division instead of chiasmata. In this case, different protein complexes are involved in the disjunction of autosomes and sex chromosomes (Arya et al., 2006).

During prophase I of meiosis, an accumulation of electron-dense filamentous structures is observed in the nuclei of primary spermatocytes. Rasmussen called these structures precursors of the central elements of the synaptonemal complex. These structures are 18 nm in diameter and are located in a less dense matrix with a space width of 90 nm. With the development of the spermatocyte cluster, these structures acquire a transverse striation and become more distinct (Rasmussen, 1973). Similar patterns were observed by Rasmussen between the conjugating homologs during meiosis in females before the formation of a typical SC (Rasmussen, 1974). This observation, however, was questioned. Carpenter (1975a) assumed that the "precursors" of the central element of SC, which were observed by Rasmussen in females, were, in fact, either a normal euchromatic SC in the sagittal section or a central element of the heterochromatic SC, or a cytochemical treatment product.

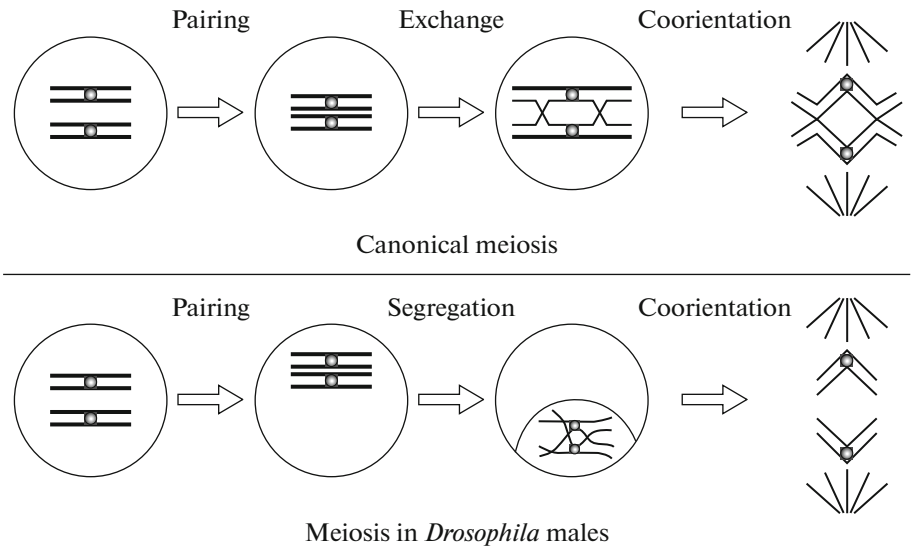

Fig. 5. Comparison of meiosis in *Drosophila* males with the canonical meiosis (by Hawley, 2002). The basic stages of meiosis (homolog pairing, exchange, chromosome coorientation, and segregation of chromosome territories) are shown.

In prometaphase I, chromosomes migrate from the periphery of the nucleus towards its center and rapidly condense. Sister chromatids at this stage are not as close to each other as in the early G_2 stages, but they remain tightly associated even in the telomeric regions. The homologous autosomes are also tightly associated (Vazquez et al., 2002).

In prometaphase I, bivalents undergo complex motions, including a short-term bipolar orientation, simultaneous reorientation of the homologous kinetochores, motions along the nuclear membrane, and motions that are not parallel to the spindle axis. It was assumed that all of these motion types are determined by the kinetochore microtubules (Church and Lin, 1985).

CONCLUSIONS

The main differences of *Drosophila* meiosis from meiosis in other organisms are listed in the introductory part of this article. Among them, the most important and unusual is the absence of crossing-over (a necessary feature of the classical meiosis) in males. Even the yeast *Schizosaccaromyces pombe*, which lack synaptonemal complexes, have meiotic recombination and crossing-over (Lorenz et al., 2006). This fundamental difference of meiosis in *Drosophila* males deserves special discussion. This is especially interesting, because the synaptonemal complexes are absent only in *Drosophila* males and because the males have the noncrossover meiosis (i.e., meiosis that is more primitive than in dividing yeast).

In all eukaryotes in which the set of meiosis-specific proteins, enzymes, and mediators of meiotic recombination was studied, this recombination begins with the programmed formation of numerous DNA double-strand breaks produced by meiosis-specific endonucleases. Thereafter, the loci of the homologous chromosomes are mutually recognized with single-strand 3' DNA ends coated with the Rad51 or Dmc1 proteins (Page and Hawley, 2004), and the formation of intermediate recombination structures (Holliday structures) begins. However, there are two organisms in which this conserved sequence of events is inverted at the very beginning: the nematode *C. elegans* and *Drosophila*. In both organisms, the synaptonemal complexes are formed first, and the endonucleases that cleave the double-stranded DNA and initiate recombination then land on their protein ultrastructural elements. This sequence of events is observed in nematodes of both sexes and in *Drosophila* females. *Drosophila* males lack synaptonemal complexes and, respectively, intranuclear ultrastructural compartments for endonuclease functioning and the initiation of the sequence of events that lead to crossing-over. The sequence of recombination processes is broken at the very beginning. Why do males lack synaptonemal complexes? It has long been established that the formation of sex in *Drosophila* obeys the so-called genetic balance, i.e., the ratio of the number of X chromosomes to the number of autosomal sets (Bridges, 1925).

In an electron-microscopic examination of *Drosophila* testes, we studied the causes of the lack of SCs in *Drosophila* males in a series of experiments; we purposefully looked for SC traits in primary spermatocytes in males and for *Drosophila* intersexes with different genomic rearrangements (Grishaeva and Bogdanov, 1986, 1988). It was established that the X chromosome of *Drosophila melanogaster* contains the genes that affect SC formation and that there is no

compensation for gene dosage in the testes during meiosis (unlike the salivary gland polytene chromosomes). Since the flies with genotypes with chromosome sets XY + 2A, X0 + 2A, and XY + 2A with duplications of the X chromosome sections 1–3A and 18A–20 were males, they were unable to form SCs. The males with duplications of sections 8C-11A were not viable, the females with the same duplication had abnormalities in the SC formation, and the females in which this region was deleted had disturbed viability and differentiation of ovarian cells. We concluded that the genes located in sections 8C-11A of the X chromosome determine for sex formation in *Drosophila* and are responsible for the SC formation (Grishaeva and Bogdanov, 1986, 1988). This region contains one of the numerator genes (*sis-A*), which transduce the signal about the chromosome ratio over the chain of genes controlling sex formation in *Drosophila* (Cline and Meyer, 1996; FlyBase). We assume that a single dose of genes located in sections 8C-11A of the X chromosome is insufficient for SC formation. However, unlike other eukaryotes, the synaptonemal complex is required for *Drosophila* (as well as for the nematode *C. elegans*) to create the intranuclear (intracellular) conditions that help to localize and accumulate enzymes that initiate the DNA double-strand breaks. Due to the lack of synaptonemal complexes and DNA double-strand breaks in males, the entire cascade of metabolic processes leading to DNA recombination and crossing-over is blocked.

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