Lecture 4.
Meiosis. Meiotic chromosomes

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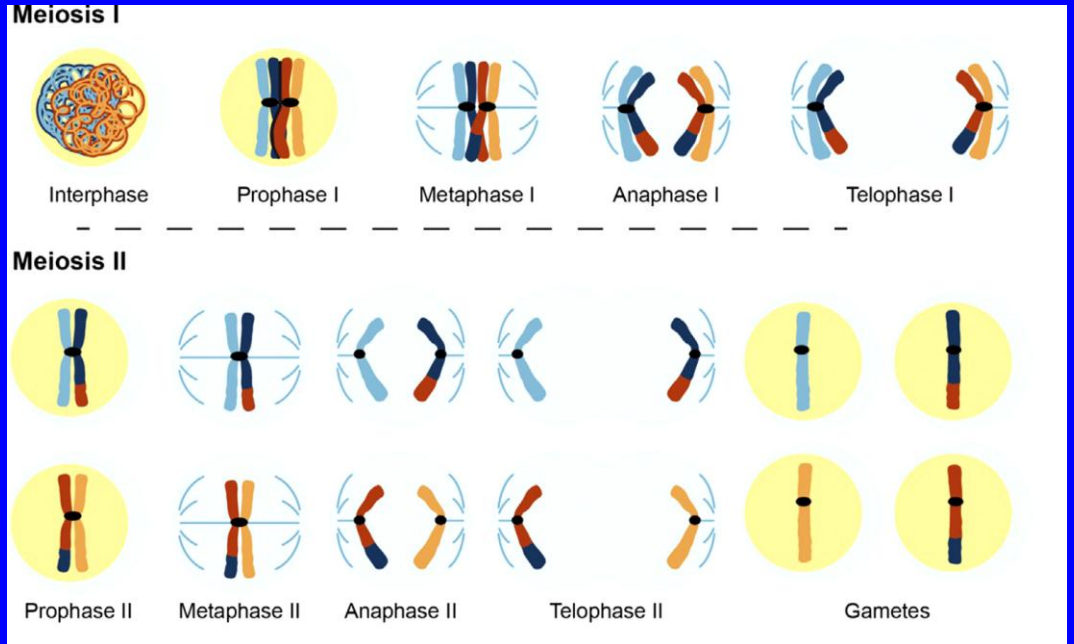
The Meiosis

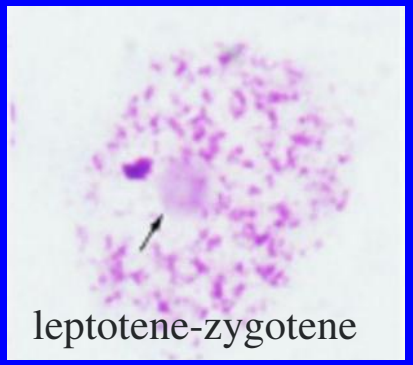
Meiosis is unique in that the S phase is followed by two meiotic divisions and produces genetically distinct cells that become the gametes. These defining features of meiosis are enabled by pairing and recombination between homologous chromosomes, which sets the stage for the two meiotic divisions. The first meiotic division is a *reductive division* that separates the homologous chromosomes while the second meiotic division is an *equational division* that results in the segregation of sister chromatids. The end products form the haploid gametes, with one copy of each homologous chromosome.



The Prophase I of Meiosis I

In ***leptotene (leptonema)***, each chromosome comprised of two chromatids. Chromosomes condense and begin to pair homologously with initiation of DNA double-strand break (DSBs) occurring. Once leptotene takes place, the cell is committed to meiosis.

In ***zygotene*** (***zygonema***) homologous chromosomes, which appear as long threadlike structures, pair locus for locus. This pairing is called synapsis. Synapsis is initiated with the formation of short lengths of the synaptonemal complex (SC). Synapsis of the X and Y chromosomes in males occurs only at the pseudoautosomal regions. These regions are located at the distal short arms and are the only segments of the X and Y chromosomes containing homologous loci. The nonhomologous portions of these chromosomes condense to form the sex vesicle. DSB repair begins.

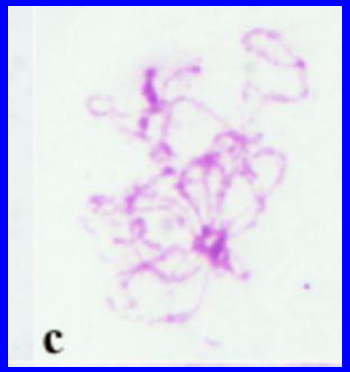

leptotene-zygotene

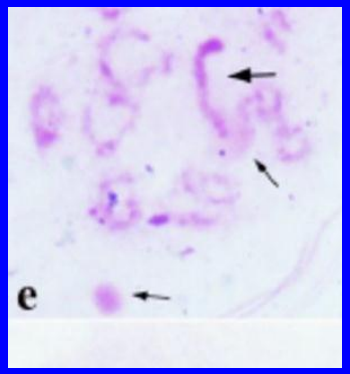
The Prophase I of Meiosis I

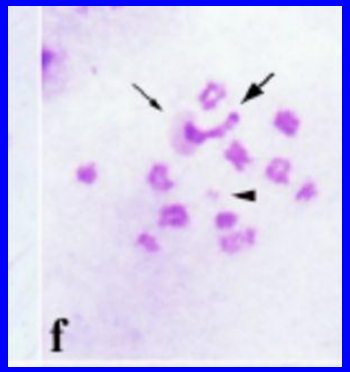
Pachynema (***pachytene***) is marked by full and homologous synapsis with SC formed along the entire length of each homologous chromosome pair. Subsets of DSBs are repaired as reciprocal ***crossover*** (COs). The paired homologs form structures called bivalents, sometimes referred to as tetrads because they are composed of four chromatids.

During ***diplonema*** (***diplotene***), the SC is disassembled and COs become visible as chiasmata holding the homologs together. In males, the sex vesicle disappears and the X and Y chromosomes associate end to end.

By ***diakinesis***, the chromosome bivalents have fully condensed and the nuclear envelope breaks down, marking metaphase when the spindle microtubules attach to nonsister kinetochores, aligning the homologous pairs on the spindle, poised for separation.





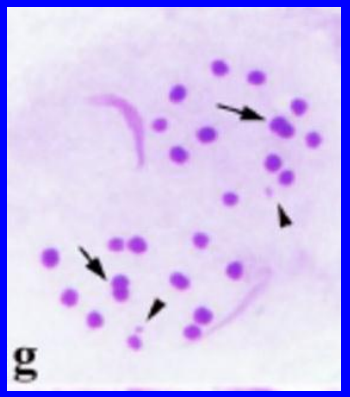


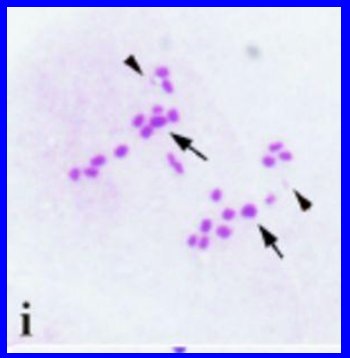
Meiosis I

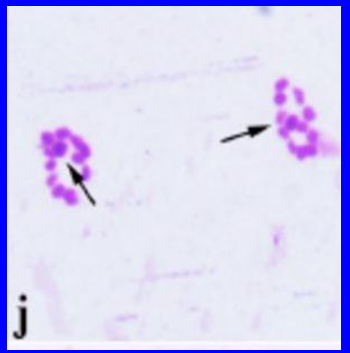
Metaphase I (g) is characterized by disappearance of the nuclear membrane and formation of the meiotic spindle. The bivalents line up on the equatorial plate with their centromeres randomly oriented toward opposite poles.

During ***anaphase I*** (i), the centromeres of each bivalent separate and migrate to opposite poles.

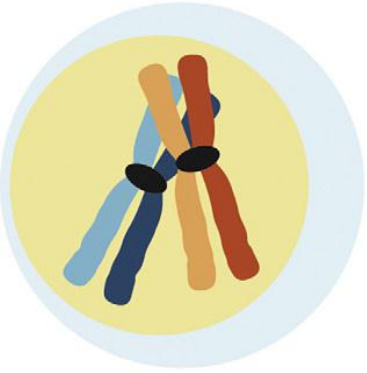
In ***telophase I*** (j), the two haploid sets of chromosomes reach opposite poles and the cytoplasm divides. The result is two cells containing 23 chromosomes (men), each composed of two chromatids.





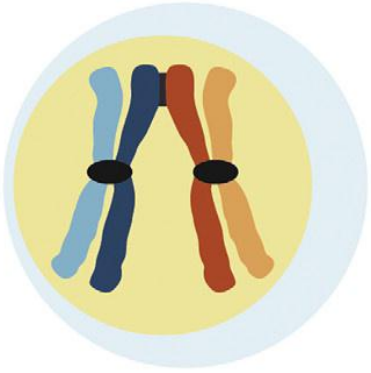


Prophase I



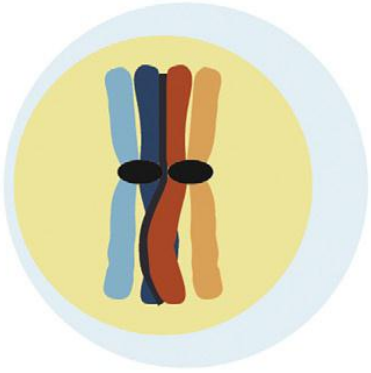
Leptonema

- Replicated homologous chromosomes condense and begin to align
- DSBs formed



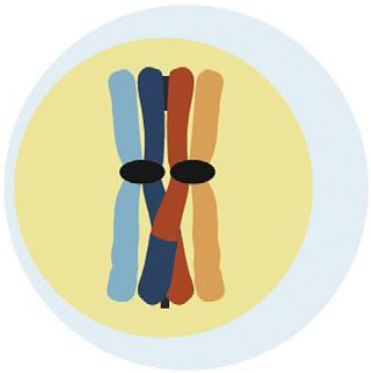
Zygonema

- Homologous pairing progresses; synapsis initiated with SC formation
- Processing of DSBs begins



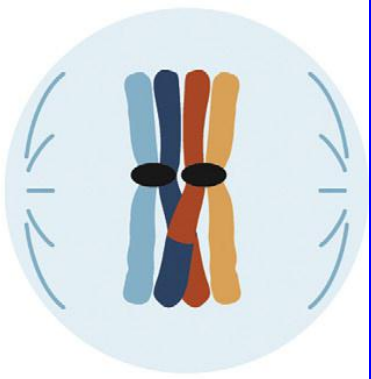
Pachynema

- Homologous chromosomes fully synapsed and SC visible
- DSBs repaired with formation of COs



Diplonema

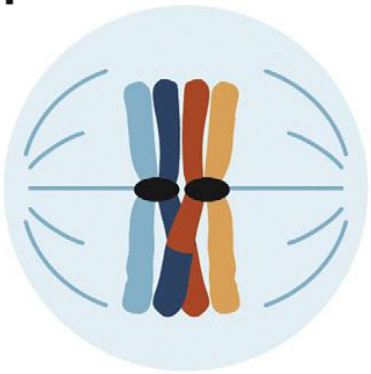
- Disassembly of SC
- Chiasmata between homologous chromosomes visible



Diakinesis

- Chromosome bivalents fully condensed
- Nuclear envelope breaks down

Metaphase I



Metaphase

- Spindle microtubules attach to nonsister kinetochores
- Tension aligns chromosome bivalents in bipolar orientation

Meiosis II

After a typically brief interphase, in which no DNA synthesis occurs, the second meiotic division begins.

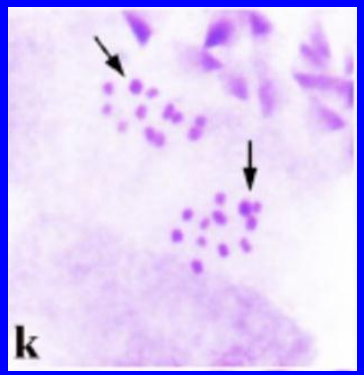
At the two poles of the cell the clusters of chromosomes enter a brief ***prophase II***, each nuclear envelope breaking down as a new spindle forms.

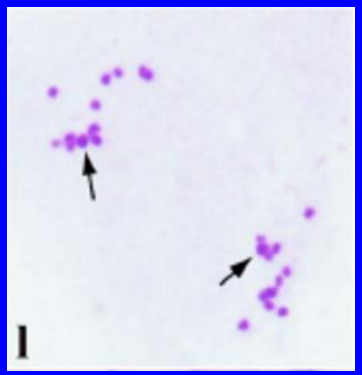
In ***metaphase II*** (k), spindle fibers bind to both sides of the centromeres.

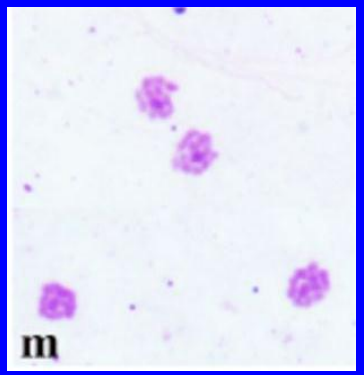
In ***anaphase II*** (l), the spindle fibers contract, splitting the centromeres and moving the sister chromatids to opposite poles.

In ***telophase II*** (m), the nuclear envelope re-forms around the four sets of daughter chromosomes.

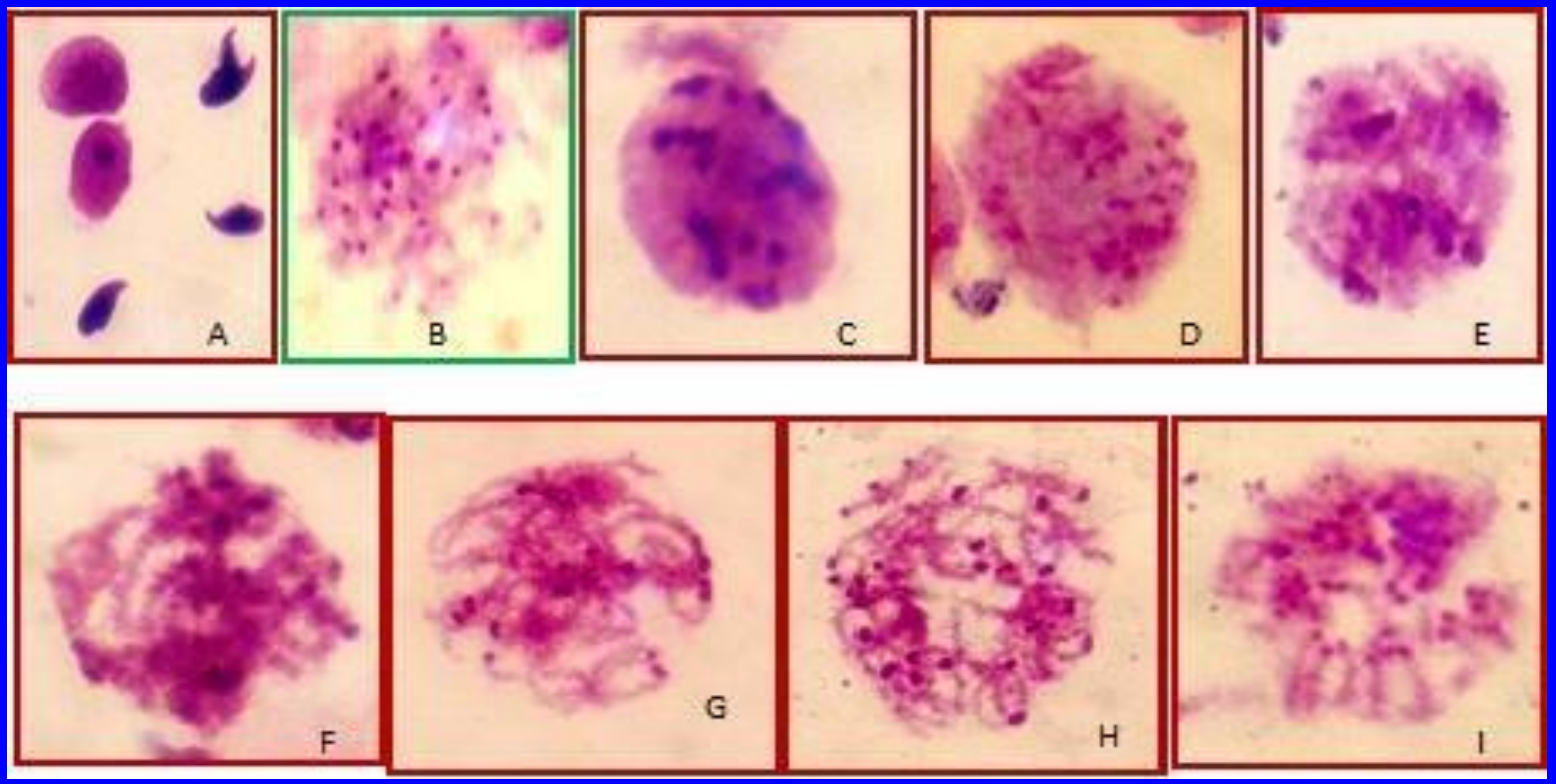
The final result of this division is four cells containing haploid sets of chromosomes. No two are alike, because of the crossing over in prophase I. Nuclear envelopes then form around each haploid set of chromosomes.





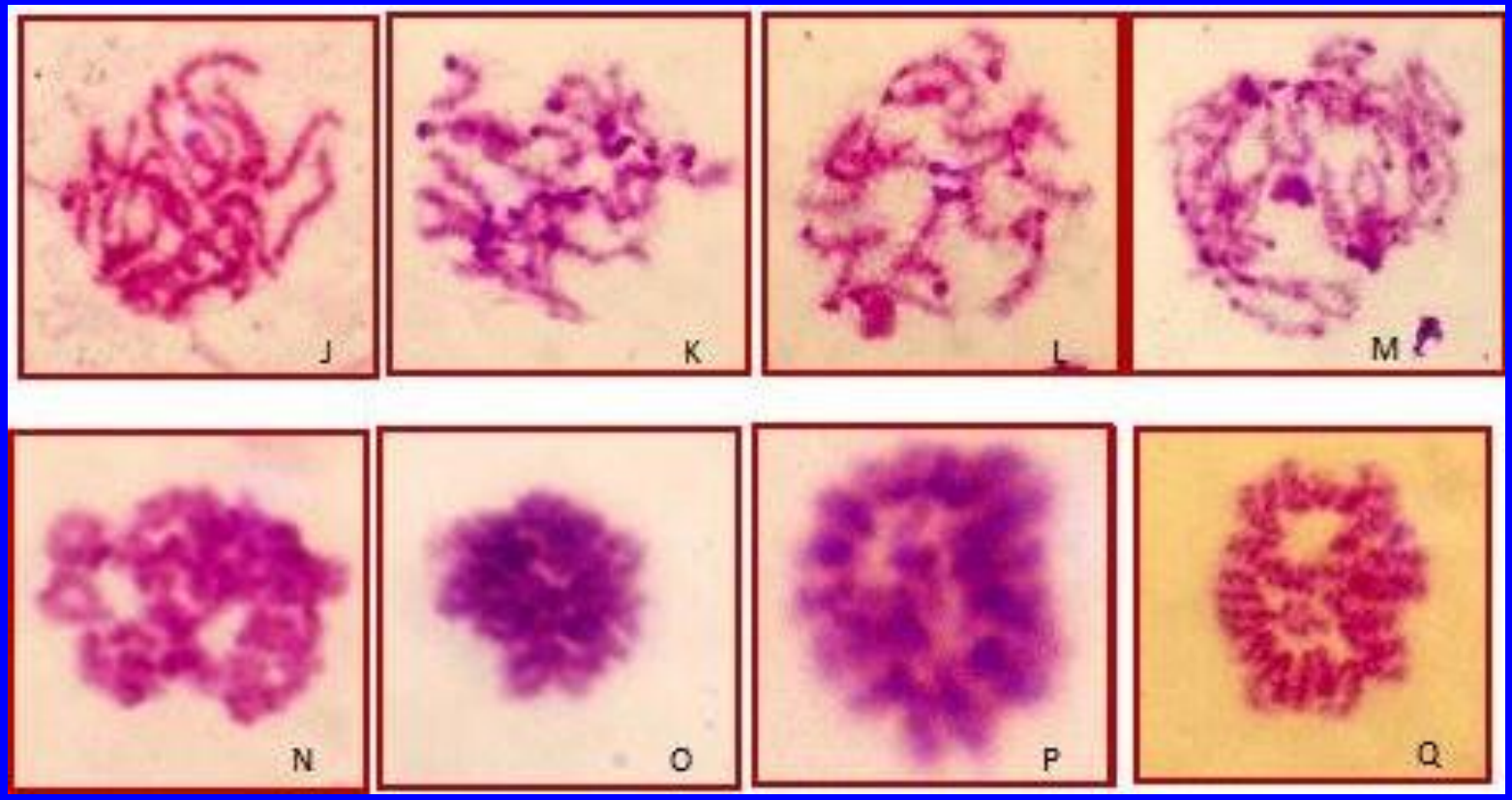


Germinal cell cycle in *Mus musculus castaneus*



A - Interphase nuclei with sperm head,
B - Somatic C-banded chromosomes,
C - Non random arrangement of chromocenters in four sites inside the nuclei,
D - Early leptotene,
E - Mid leptotene,
F - Late leptotene,
G - Early zygotene with bivalents showing synapsis,
H - Mid zygotene,
I - Late zygotene

Germinal cell cycle in *Mus musculus castaneus*



J - Early pachytene,
K - Mid pachytene,
L - Late pachytene and the sex chromatin is at the periphery,
M - Diplotene cell ,
N-, O- Diakenesis showing congregations of tetravalents,
P - Metaphase I the chromosomes are arranged in a circular manner,
Q - Metaphase II arrangement is just like that of Metaphase I.

MEIOTIC PROPHASE CHROMOSOME DYNAMICS: THE FOUNDATION OF MEIOSIS

At the heart of meiosis are the unique events in the first prophase:

- ✓ initiation of a meiotic (rather than mitotic) division,
- ✓ homologous chromosome pairing,
- ✓ molecular recombination between homologous (but nonsister) chromatids.

These processes are initiated by gonadal signals and orchestrated by unique aspects of chromosomal axes (synaptonemal complex)

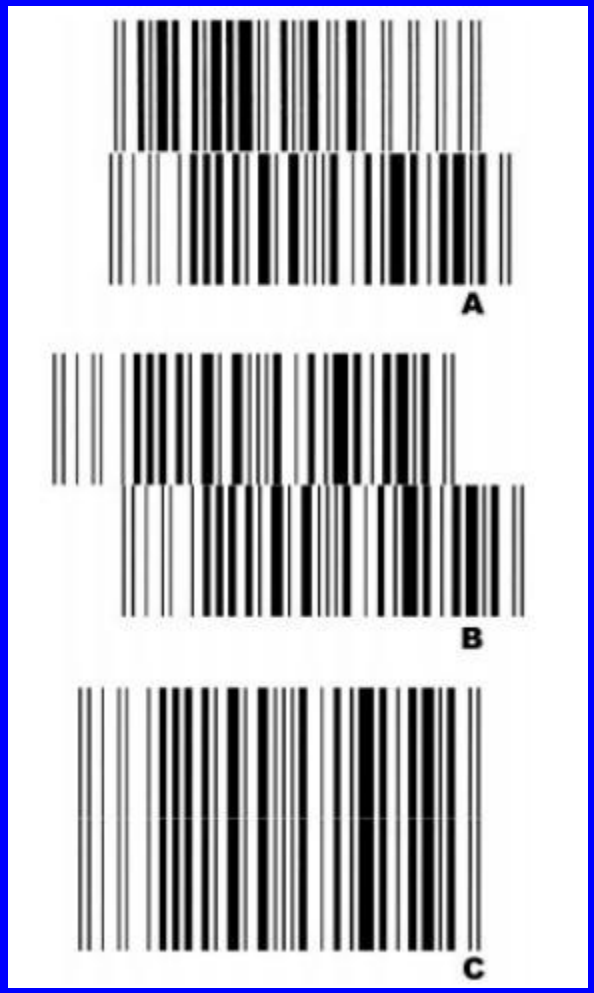
INITIATION OF MEIOSIS IN GERM CELLS

The morphogen ***retinoic acid*** (RA), the active metabolite of vitamin A (retinol), initiates the meiotic program of germ cells, albeit in a sexually dimorphic manner. Retinol, which is of broad developmental significance, is widely available throughout the body via the circulatory system and is transported into target cells, where it undergoes a two-step enzymatic conversion to retinaldehyde and RA. An important target for RA action on meiosis in the mouse is the gene ***Stra8*** (stimulated by retinoic acid, gene 8). Thus, the onset of meiosis in germ cells of both sexes is dependent on expression of the STRA8 protein.

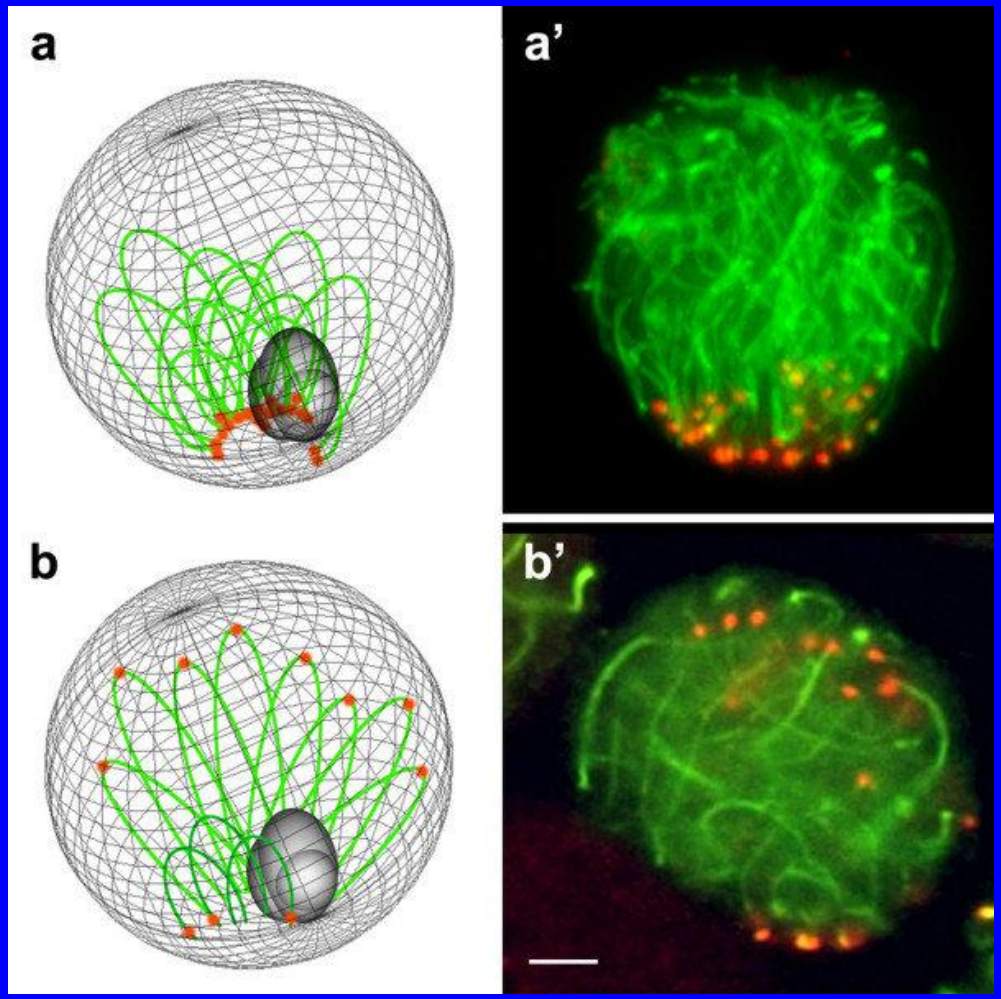
Genetic analyses suggest that STRA8 is a key activator of downstream genes required for multiple aspects of meiosis, including chromosome dynamics and recombination. STRA8 may also function as a switch between the mitotic and meiotic cell cycle programs, suggested by the finding that one gene it activates is ***Meioc*** (Meiosis-specific with coiled-coil domain), which is critical for the extended meiotic prophase required to complete chromosome dynamics and meiotic recombination processes. ***MEIOC*** may act by preventing degradation of transcripts of genes essential for meiotic prophase.

HOMOLOGOUS INTERACTIONS OF MEIOTIC CHROMOSOMES

The cohesin axes are assembled concurrently with, and facilitate, the processes by which meiotic chromosomes find each other and undergo homologous pairing. The concept of a chromosome "***bar code***" is a mechanism mediating the homology search and recognition process, and this might be based on the proteins composing the axis. For example, the meiosis-specific cohesin complex proteins REC8 and RAD21L have mutually exclusive localization along the chromosomal axis, potentially providing such a bar code for homology recognition.



HOMOLOGOUS INTERACTIONS OF MEIOTIC CHROMOSOMES



Berrios S., 2013

In germ cells, chromosomal telomeres exhibit dynamic movement and tethering to the nuclear envelope at the preleptotene stage, forming a cluster termed the "***bouquet***", which facilitates homologous interactions between chromosomes. Clustering of chromosome ends has the effect of reducing the size of nuclear space that must be searched for homology recognition.

Cell

Volume 125, Issue 1, 7 April 2006, Pages 19-21

Preview

The Meiotic Chromosomal Bouquet: SUN Collects Flowers

Kazunori Tomita [1], Julia Promisel Cooper [1]

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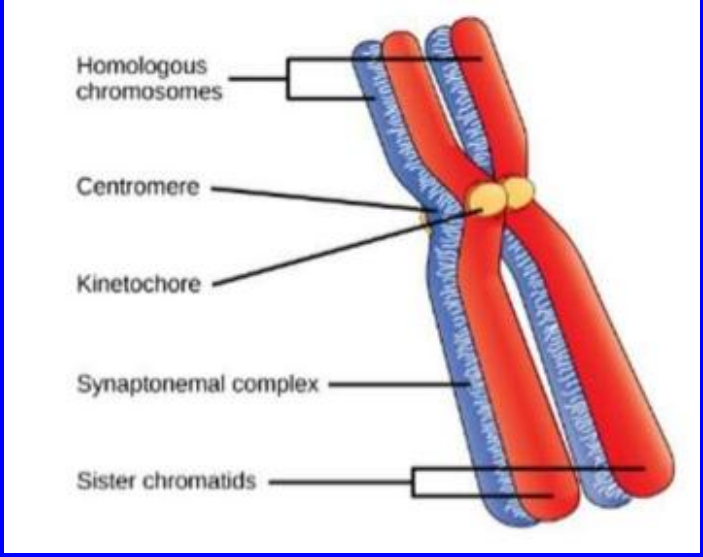
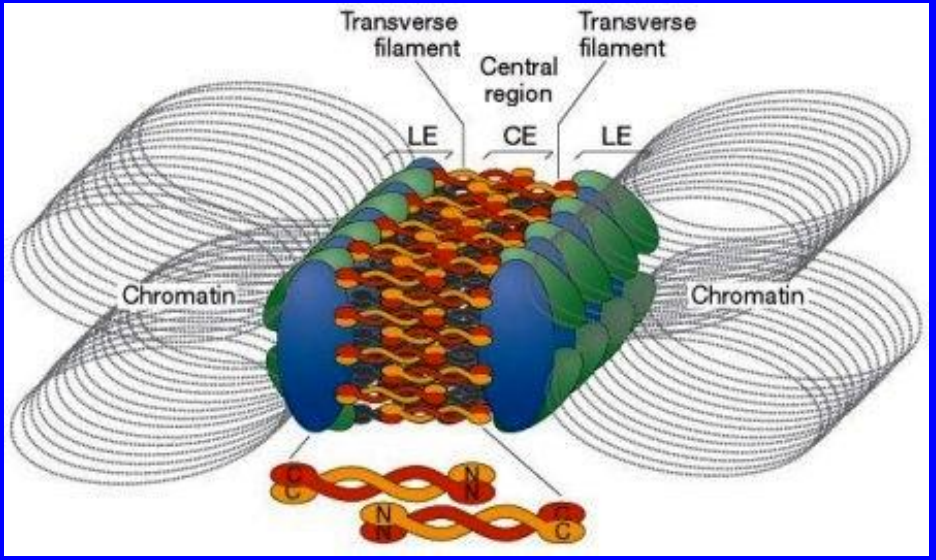
https://doi.org/10.1016/j.cell.2006.03.020

SYNAPTONEMAL COMPLEX

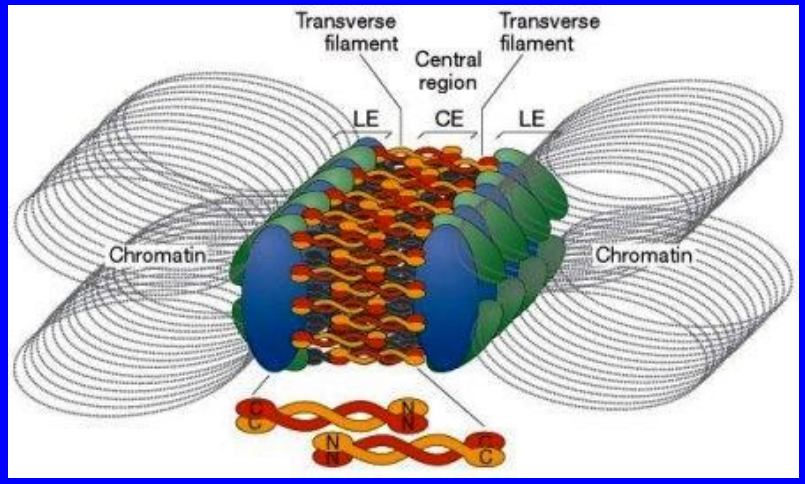
Meiotic chromosome synapsis during prophase I is mediated by the synaptonemal complex (SC). ***Synaptonemal complexes (SCs)*** are zipper-like structures which are assembled between homologous chromosomes during the prophase of the first meiotic division. Their assembly and disassembly correlate with the successive chromatin rearrangements of meiotic prophase, namely the condensation, pairing, recombination and disjunction of homologous chromosomes. SCs are considered to be structures that both control the number and distribution of reciprocal exchanges between homologous chromosomes (cross-overs) and convert cross-overs into functional chiasmata.

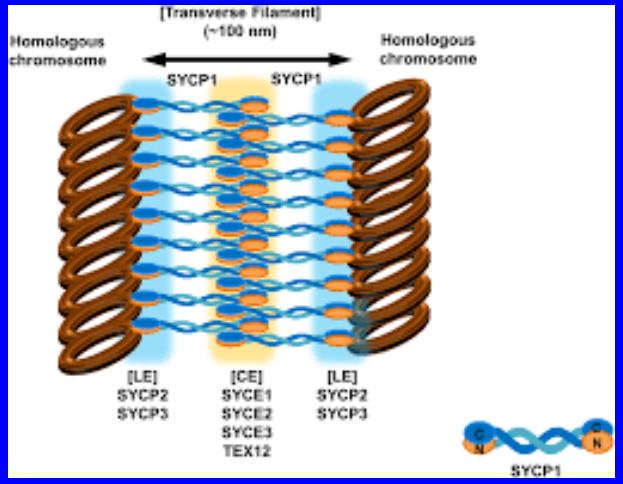


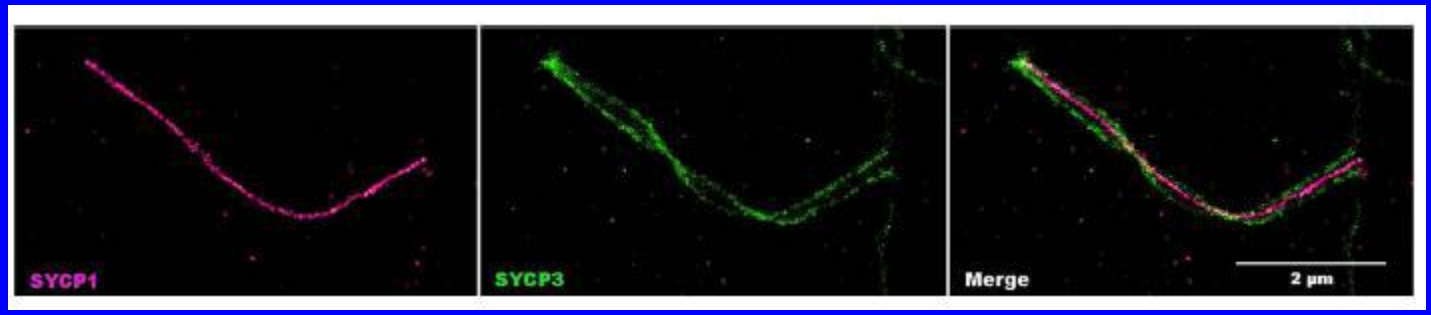


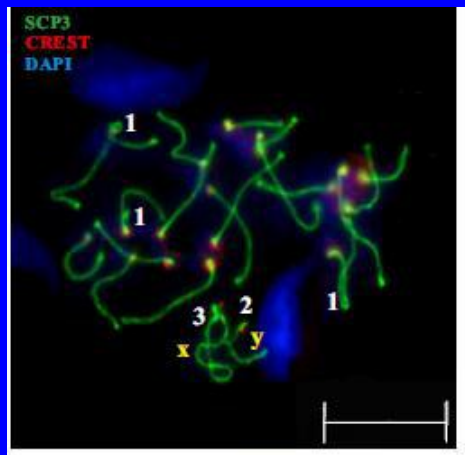
SYNAPTONEMAL COMPLEX

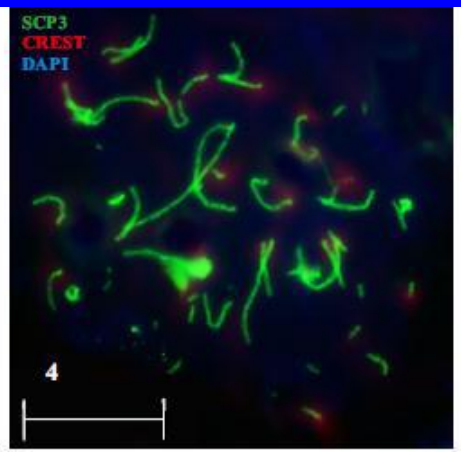
Incorrect chromosome synapsis impairs homologous recombination leading to chromosome missegregation (aneuploid gametes) or cell death (infertility). Therefore, proper assembly of the SC is required for successful meiosis and production of healthy germ cells.

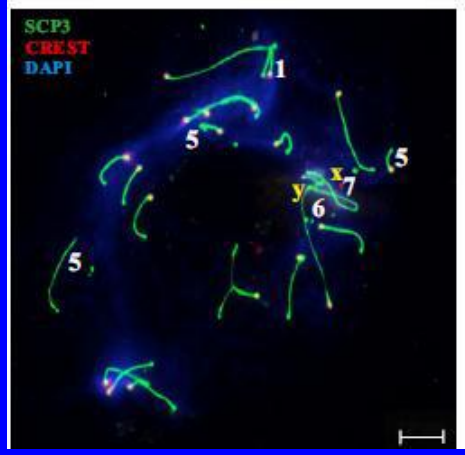


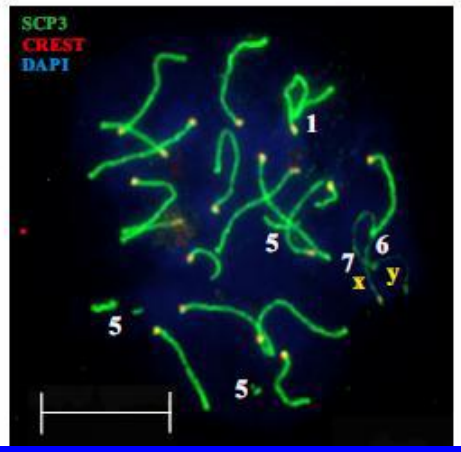












Immunostaining with antibodies to SC - SCP3 (green) protein, antibodies with centromeres - CREST (red). Chromatin is stained with DAPI (blue), x1000, Bar = 10 μm:

XY - sexual bivalent; 1 - atypical structure of the SC, 2 - desynapsis of sex chromosomes,

3 – ring X chromosome; 4 - multiple fragmentation (meiotic "catastrophe");

5 - single fragments; 6 - association of autosomes with the XU bivalent, 7 - violation of the formation of the “sex vesicle”

MEIOTIC RECOMBINATION

Recombination is event of the first meiotic prophase, plays out in synchrony with axis formation, homology recognition, and synapsis. Aside from its genetic function to create diversity with new and shuffled gene allele combinations, meiotic recombination serves the important cell biological function of creating the linkages between homologous chromosomes that are required for their accurate separation (or "segregation") from each other, thereby ensuring accuracy of Meiosis I. Aneuploidy and loss of genomic integrity are frequently the penalties of meiotic recombination gone wrong.

The three major **phases** of recombination in mammals:

(1) activation of recombination sites by PRDM9 (PR domain containing 9),

(2) formation of DNA DSBs by SPO11 (SPO11 meiotic protein covalently bound to DSB),

(3) DSB repair and Crossover (CO) by the many proteins.

MEIOTIC RECOMBINATION

1. Activation of Meiotic Recombination.

Meiotic recombination is a chromatin-associated process that generally is limited to specific genomic locations called hotspots (HS). In humans and mice, the HS are determined and activated by the DNA-binding, zinc finger PRDM9 protein.

2. Formation of DSBs.

The second crucial step of recombination is creation of DSBs at the activated HS. This is accomplished by SPO11, a conserved topoisomerase, in association with TOPOVIBL (TopoVI DNA topoisomerase B like).

There are two isoforms of SPO11: SPO11A (involved in catalyzing DSBs in the pairing region of the X and Y sex chromosomes) and SPO11B (involved in global DSB formation). A multiprotein complex, known as the recombinosome, is required for SPO11-mediated DSB formation. The recombinosome, a structure that assembles and evolves in its protein components during early meiotic prophase, is formed by MEI4 (meiotic doublestranded break formation protein 4) and REC114 (meiotic recombination protein).

MEIOTIC RECOMBINATION

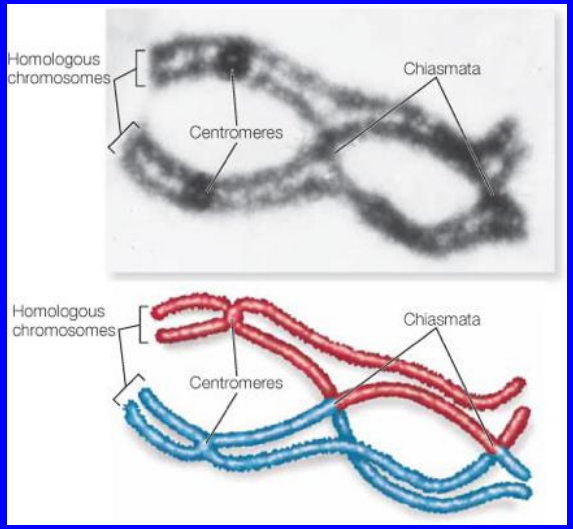
3. Repair of DSBs and CO.

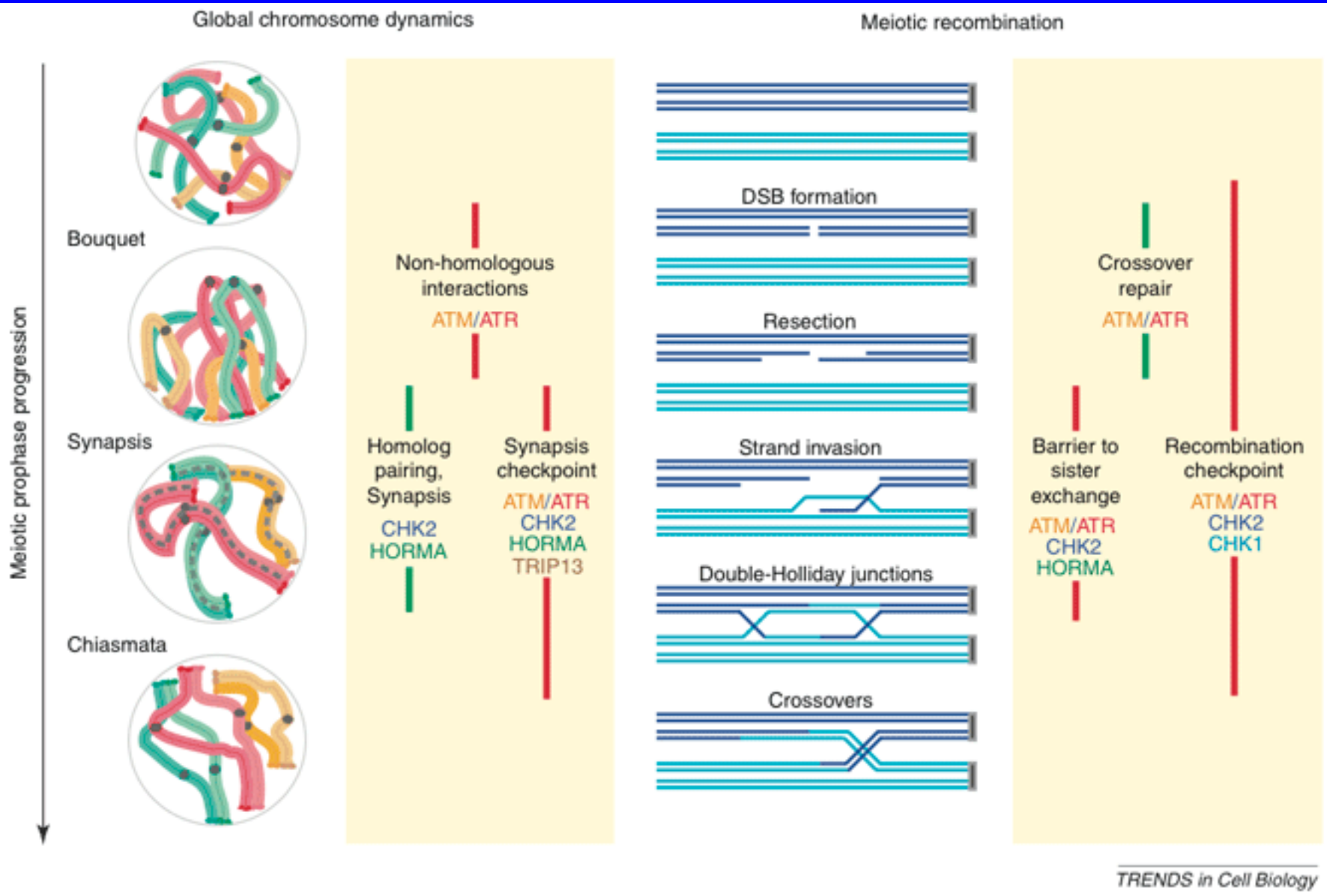
The third important step of meiotic recombination is repair of the DSBs and their resolution as either ***reciprocal recombination crossovers*** (COs) or ***noncrossover events*** (NCOs).

COs are the outcome of homologous recombination whereby single-stranded DNA ends from a DSB invade a homologous (but nonsister) chromatid, using it as a repair template. This repair event forms the interhomolog connections visualized as ***chiasmata*** during Meiosis I. Number of chiasmata usually depend upon the length of chromosome

NCO-associated repair mechanisms involve synthesis-dependent strand annealing with a sister chromatid as the repair template, leading to gene conversion events.

Of the large number of DSBs created in early prophase (250–300 in mice), only about 10% are resolved as COs while the remainder are repaired as NCOs.





TRENDS in Cell Biology

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