

Meiosis, its regulation and disturbances

Meiosis is a type of cell division that reduces the number of chromosomes in the parent cell by half and produces four gamete cells. In contrast to mitosis, meiosis consists of one round of DNA replication followed by two rounds of chromosome segregation and cell division. During meiosis I, homologous chromosomes pair and separate. During meiosis II, the sister chromatids of each duplicated chromosome separate. Meiosis generates gamete genetic diversity in two ways: (1) Law of Independent Assortment. The independent orientation of homologous chromosome pairs along the metaphase plate during metaphase I & orientation of sister chromatids in metaphase II allows a random and independent distribution of chromosomes to each daughter cell (and ultimately to gametes); and (2) Crossing Over. The physical exchange of homologous chromosomal regions by homologous recombination during prophase I results in new combinations of DNA within chromosomes.

The phases of meiosis:

1. Meiosis I

Meiosis I is also known as the reduction division, because it is the division in which the chromosome number is reduced by half through the pairing of homologues in prophase and by their segregation to different cells at anaphase of meiosis I.

- a) prophase I : Prophase I is typically the longest phase of meiosis. Prophase I has been divided into a series of substages which are named according to the appearance of chromosomes.

• **Leptotene:** Leptotene is the first stage of meiosis. This is also the first step in the condensation of DNA, a phenomenon that proceeds through the entire prophase I. Individual chromosomes—each consisting of two sister chromatids—form visible strands within the nucleus. The two sister chromatids closely associate and are visually indistinguishable from one another. The homolog chromosomes are still unpaired. • **Zygotene:** The zygotene stage occurs as the chromosomes approximately line up with each other into homologous chromosome pairs. At this stage, the synapsis of homologous chromosomes takes place. Individuals of a pair are equal in length and in position of the centromere. Thus pairing is highly specific and exact. The paired chromosomes are called bivalent or tetrad chromosomes.

• **Pachytene:** This is the stage when homologous recombination, including chromosomal crossover (crossing over), occurs. Nonsister chromatids of homologous chromosomes may exchange segments over regions of homology. At the sites where exchange happens, chiasmata form.

• **Diplotene:** During the diplotene stage, the synaptonemal complex degrades and homologous chromosomes separate from one another a little. However, the homologous chromosomes of each bivalent remain tightly bound at chiasmata, the regions where crossing-over occurred. The chiasmata remain on the chromosomes until they are severed at the transition to anaphase I.

• **Diakinesis:** Chromosomes condense further during the diakinesis stage. This is the first point in meiosis where the four parts of the tetrads are actually visible. Sites of crossing over entangle together, effectively overlapping, making chiasmata clearly visible. The nucleoli disappear, the nuclear membrane disintegrates into vesicles, and the meiotic spindle begins to form.

- b) metaphase I: As kinetochore microtubules from both centrosomes attach to their respective kinetochores, the paired homologous chromosomes align along an equatorial plane. In meiosis, establishing tension requires at least one crossover per chromosome pair in addition to cohesin between sister chromatids.
- c) anaphase I: The homologues of each bivalent separate and move to opposite poles, but sister chromatids do not separate. Kinetochore microtubules shorten, pulling homologous chromosomes (which consist of a pair of sister chromatids) to opposite poles. Nonkinetochore microtubules lengthen, pushing the centrosomes farther apart. The cell elongates in preparation for division down the center. Unlike in mitosis, only the cohesin from the chromosome arms is degraded while the cohesin surrounding the centromere remains protected. This allows the sister chromatids to remain together while homologs are segregated. The cohesion is eliminated by the proteolytic cleavage by the protease separase. Separase is held inactive until the onset of anaphase through its binding to the inhibitor protein securin. At the onset of anaphase I, anaphase promoting complex (APC) becomes active and ubiquitylates securin, thereby targeting it for destruction. Active separase now cleaves the subunit of cohesin on the chromosome arms, which triggers the separation of homologues to opposite poles of the meiosis-I spindle.
- d) telophase I: The first meiotic division effectively ends when the chromosomes arrive at the poles. Each daughter cell now has half the number of chromosomes but each chromosome consists of a pair of chromatids. The microtubules that make up the spindle network disappear, and a new nuclear membrane surrounds each haploid set. The chromosomes uncoil back into chromatin. Sister chromatids remain attached during telophase I.

Meiosis II

Meiosis II is the second meiotic division, and usually involves equational segregation, or separation of sister chromatids. Mechanically, the process is similar to mitosis, though its genetic results are fundamentally different.

- a) prophase II: The cells have one chromosome from each homologous pair. We see the disappearance of the nucleoli and the nuclear envelope again as well as the shortening and thickening of the chromatids. Centrosomes move to the polar regions and arrange spindle fibers for the second meiotic division.
- b) metaphase II: Chromosomes align at the metaphase plate. The centromeres contain two kinetochores that attach to spindle fibers from the centrosomes at opposite poles. The new equatorial metaphase plate is rotated by 90 degrees when compared to meiosis I, perpendicular to the previous plate. At metaphase II, kinetochores are bi-oriented and separase is once again inhibited by securin.
- c) anaphase II: At the onset of anaphase II separase once again becomes active and it triggers the segregation of sister chromatids to opposite poles. Sister chromatids separate and become daughter chromosomes, in which the remaining centromeric cohesin is cleaved allowing the sister chromatids to segregate.
- d) telophase II: Spindle disappears, nuclei form, and cytokinesis takes place. It is marked by decondensation and lengthening of the chromosomes and the disassembly of the spindle. Nuclear envelopes reform and cleavage or cell plate formation eventually produces a total of four daughter cells, each with a haploid set of chromosomes.

Meiotic disturbances

The normal separation of chromosomes in meiosis I or sister chromatids in meiosis II is termed disjunction. When the segregation is not normal, it is called nondisjunction. This results in the production of gametes which have either too many or too few of a particular chromosome, and is a common mechanism for trisomy or monosomy. Most monosomic and trisomic human embryos are not viable, but some aneuploidies can be tolerated, such as trisomy for the smallest chromosome, chromosome 21 (Down syndrome). Phenotypes of these aneuploidies range from severe developmental disorders to asymptomatic. The probability of nondisjunction in human oocytes increases with increasing maternal age, presumably due to loss of cohesin over time. The propensity of a chromosome pair to nondisjoin has been strongly associated with aberrations in the frequency or placement, or both, of recombination events in meiosis I, which are critical for maintaining proper synapsis. A chromosome pair with too few (or even no) recombinations, or with recombination too close to the centromere or telomere, may be more susceptible to nondisjunction than a chromosome pair with a more typical number and distribution of recombination events. Meiotic regulation -> Meiotic CDKs direct chromosome segregation during meiosis I. In the frog (*Xenopus laevis*), meiotic CDKs are partially inactivated between meiosis I and meiosis II, which prevents further DNA replication and chromosome segregation. Meiotic CDK activity rises again to allow entry into meiosis II. Complete inactivation of meiotic CDKs triggers exit from meiosis II.