

What unique chromosomal events lead to the formation of a haploid male germ cell?

M.A. Handel

Meiosis is a unique and defining event of gametogenesis serving at least two functions in the reproductive life cycle: it reduces chromosome number to the haploid state in the gamete (thus allowing diploidy to be restored at fertilization), and it shuffles gene allele combinations, giving rise to genetic diversity. Meiosis is accomplished in two remarkably coordinated divisions, without an intervening S phase (Fig. 1). The first division, a reductional division, segregates the homologous chromosomes into separate cells, and the second division, an equational division, reduces the DNA content to haploidy. The success of these divisions depends on the unique dynamics of chromosomes during the extended meiotic prophase.

Meiosis is initiated after mitotic proliferation of spermatogonia by DNA synthesis that accomplishes precise replication of each chromosome to form two chromatids. Thus the DNA content ("C" value) has doubled from 2C to 4C, but the chromosome number ("N" value) of the germ cell is not changed – it is still the 2N diploid value, e.g., 46 chromosomes in humans (note: spermatocytes are not tetraploid). During meiosis I prophase, homologous chromosomes pair, forming bivalents, undergo recombination – these are defining events of meiosis and key features that distinguish meiosis from mitosis. Meiotic prophase I is divided into substages that mark the dynamics of chromosome behavior. During the leptotene stage, chromosomes are subject to endogenous double-strand DNA breaks, mediated by the SPO11 enzyme, that initiate the molecular events of meiotic recombination. Also during the leptotene phase, homologous chromosomes find each other by homology searching mechanisms that are not well understood, but may be facilitated by telomere clustering into a "bouquet" on the nuclear envelope and/or the DNA breaks and subsequent formation of short single-stranded ends. During the zygotene stage, chromosome pairing extends and homologs become intimately associated by synapsis, a process mediated by the synaptonemal complex (SC).

The SC is a protein complex comprised of lateral elements that form the scaffold, or axes, of each homolog, and a central element that is structural "glue" mediating complete synapsis. The completion of synapsis marks the beginning of the pachytene stage, which is lengthy (approximately 16 days in the human) and characterized by considerable growth of the spermatocyte as well as by important chromosome dynamics. Now the chromosomes are visualized as homologous pairs, called bivalents, e.g., 23 bivalents in

humans. Notably, however, the non-homologous X and Y chromosomes are synapsed only in a small region of homology (the pseudo-autosomal region) and are sequestered in a heterochromatic nuclear domain known as the XY body (or sex body). During the pachytene stage, molecular events of homologous recombination unfold. Interestingly, the number of recombination-initiating double-strand breaks is in approximately ten-fold excess to the number of final reciprocal recombinations (crossovers), which is always at least one per chromosome, but can be up to two or three in longer chromosomes. The excess DNA double-strand breaks are thought to be repaired by a recombination mechanism that involves non-crossover gene conversion, or site-specific exchange of information without exchange of surrounding chromosomal regions.

The completion of recombination marks the passage of the germ cell into the final, diplotene, stage of meiosis I prophase, when the chromosomes undergo desynapsis and condense. At this stage, the homologs are still held together by the recombination sites (crossovers), visibly manifest as chiasmata. The chiasmata serve the essential function of maintaining the homologous pairs in a bi-polar orientation as they line up on the spindle apparatus at metaphase of the first meiotic division. The first meiotic division is reductional, separating the members of each homologous pair. The result is two cells, secondary spermatocytes, each with the haploid chromosome content (e.g., 23 chromosomes in humans), but with each chromosome still comprised of two chromatids. The meiosis II division ensues rapidly and is an equational division much like mitosis, separating the chromatids to separate cells, each of which now contains the haploid 1N chromosome number (e.g., 23 chromosomes in humans) and 1C DNA content. Similar to the mitotic divisions of differentiated spermatogonia, the two meiotic divisions are characterized by incomplete cytokinesis and the persistence of intercellular bridges. Thus, when meiosis is completed, the haploid round spermatids are conjoined in a syncytium as they commence the differentiation process of spermiogenesis.

Much attention has been directed to how the meiotic choreography of chromosome movement and the processes of recombination can go wrong, and whether these errors can explain any cases of human infertility. The penalty of errors is germ-cell arrest or generation of aneuploid gametes and offspring, bearing the wrong number of chromosomes. Both failure of recombination and chiasmata formation or abnormal persistence of chiasmata can negatively impact fidelity of chromosome segregation during the first meiotic division by causing nondisjunction (failure of homologs to separate to the two spindle poles). Likewise, absence or persistence of sister chromatid cohesion can cause abnormalities in chromosome segregation. Screening infertile men for gametic aneuploidy by monitoring sperm

chromosome content using fluorescent in situ hybridization (FISH) has failed to find strongly significant correlations between infertility and production of aneuploid sperm, and, indeed, meiotic nondisjunction is less frequent in the human male than in the female. However, infertility due to arrested spermatogenesis and germ cell death is a common phenotype in mouse models lacking proteins involved in meiotic recombination. Although similar mutations have been found among infertile males, causality is difficult to establish. Nonetheless, it can be anticipated that the advent of personal genome sequencing will facilitate the identification of meiosis mutations in humans.

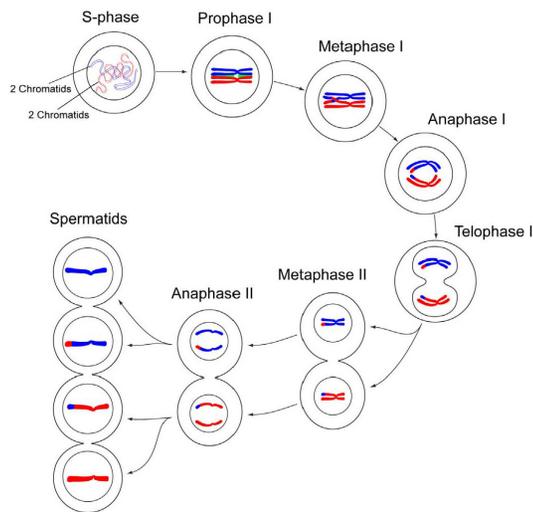


FIG. 1. This diagram illustrates the sequence of key events of meiosis in male germ cells. Red and blue depict the two homologs of an autosomal chromosome, one maternally derived and the other paternally derived. At the completion of S-phase, each chromosome consists of two chromatids. At the pachytene stage of prophase I, homologs are synapsed to form a bivalent, an event mediated by the synaptonemal complex (green). By metaphase I, chiasmata, the visible manifestation of recombination events, are seen. In anaphase I and telophase I, the homologs separate from each other, reducing the chromosome number to the haploid content. Spermatocytes rapidly progress to metaphase II, and subsequently the chromatids are separated in anaphase II, to form the 4 haploid spermatids.

In summary, meiosis is a defining event of spermatogenesis and is comprised of two divisions (Fig. 1). The events of meiosis I prophase include

pairing and synapsis of homologous chromosomes and reciprocal recombination, resulting in new combinations of gene alleles. The first of the two meiotic divisions is a reductional division, separating homologous chromosomes and reducing chromosome number from 2N to 1N. The second division is equational, separating chromatids. The products of these meiotic divisions are 4 spermatids, each with the haploid 1N chromosome number and 1C DNA content.

Suggested reading

- Cohen PE, Pollack SE, Pollard JW. Genetic analysis of chromosome pairing, recombination, and cell cycle control during first meiotic prophase in mammals. *Endocr Rev.* 2006; 27:398-426.
- Handel MA, Schimenti JC. Genetics of mammalian meiosis: regulation, dynamics and impact on fertility. *Nat Rev Genet.* 2010; 11: 124-36.
- Hassold T, Hall H, Hunt P. The origin of human aneuploidy: where we have been, where we are going. *Hum Mol Genet.* 2007; 16 (Review Issue 2): R203-R208.