Oocyte Development, Meiosis and Aneuploidy

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Review

Oocyte development, meiosis and aneuploidy

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ABSTRACT

Meiosis is one of the defining events in gametogenesis. Male and female germ cells both undergo one round of meiotic cell division during their development in order to reduce the ploidy of the gametes, and thereby maintain the ploidy of the species after fertilisation. However, there are some aspects of meiosis in the female germline, such as the prolonged arrest in dictyate, that appear to predispose oocytes to missegregate their chromosomes and transmit aneuploidies to the next generation. These maternally-derived aneuploidies are particularly problematic in humans where they are major contributors to miscarriage, age-related infertility, and the high incidence of Down's syndrome in human conceptions. This review will discuss how events that occur in foetal oocyte development and during the oocytes' prolonged dictyate arrest can influence meiotic chromosome segregation and the incidence of aneuploidy in adult oocytes.

Contents

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1. Introduction

Abnormalities in chromosome number, or aneuploidies, have been associated with human disease for over fifty years, and are the most common known genetic cause of developmental and intellectual disabilities in human births [1–5]. Embryos ought to inherit one copy of each of the twenty two autosomes and one sex chromosome from each parent, and aneuploidy can involve inheriting too many or too few of any of these chromosomes. Most aneuploid embryos that inherit only one copy of an autosome (autosomal monosomy) develop severe abnormalities and die before pregnancy is clinically recognised. Inheriting an extra copy of an autosome (autosomal trisomy) is also associated with severe developmental abnormalities and accounts for approximately a third of all miscarriages. Some autosomal trisomies, and some sex chromosome aneuploidies, are compatible with birth in humans. Chromosome 21 trisomy, the cause of Down's syndrome, is by far the most frequent aneuploidy affecting live births [4–6].

Aneuploid embryos arise primarily due to inheritance of maternally-derived aneuploidies: around 10–30% of fertilised oocytes are aneuploid, compared to only 1–2% of spermatozoa [4–6]. This strong maternal bias applies primarily to autosomal aneuploidies, but sex chromosome aneuploidies are exceptions to this: the extra sex chromosome that causes Klinefelter's syndrome (XXY sex chromosome trisomy) is paternally derived in 46% of cases [4]. Down's syndrome does follow the general maternal bias for aneuploidy with around 88% of chromosome 21 trisomies arising maternally, 8% paternally, and the remainder thought to arise due to mitotic errors during early embryonic development [4]. The frequency of aneuploid conceptions is strongly associated with maternal age, and aneuploidy rates increase exponentially during the decade prior to menopause. Maternal age affects autosomes more strongly than sex chromosomes, and some autosomes more strongly than others [4–6]. The high prevalence and severe consequences of oocyte aneuploidy make maternally-derived aneuploidy a subject of significant importance. This review will discuss recent developments in the field that inform on the causes of oocyte aneuploidy in mammals.

2. Overview of oocyte development

Mammalian oogenesis begins with the differentiation of oocytes from sexually dimorphic primordial germ cells in the foetal ovaries. In female mice, germ cells become committed to differentiate down a female pathway into oocytes between E12.5 and E13.5, which is typically accompanied by a transition from mitosis to meiosis [7,8]. Meiosis involves one round of DNA replication followed by two meiotic divisions, MI and MII [6,9–12]. Oocytes initiating meiosis contain two homologous copies of each chromosome, one inherited from each parent, each of which replicates to form two sister chromatids during meiotic S phase, and are held together by sister chromatid cohesion. After meiotic S phase, oocytes enter the leptotene stage of MI, and initiate meiotic recombination by generating DNA double strand breaks (DSBs) that recruit repair proteins to form recombination foci [13]. This stimulates the pairing and synapsis of homologous chromosomes in zygotene as DSBs search for a homologous template to repair from. Synapsis and assembly of the synaptonemal complex, a protein scaffold that holds synapsed chromosomes together, is complete by pachytene (Fig. 1). During zygotene and pachytene, the recombination foci mature, and recruit a series of factors that promote the resolution of recombination intermediates into either crossover or non-crossover exchanges [13]. Non-crossover exchanges only acquire short patches of homolog sequence used as a template to repair the DNA damage, whereas crossovers exchange the chromatid arms between homologous chromatids distal to the crossover site (Fig. 1). These crossover events have two purposes: they increase genetic diversity in the population; and, once the synaptonemal complex disassembles in diplotene, they provide the physical connection that keeps homologous chromosomes together [11,12]. Around the time of birth, developing oocytes arrest at dictyate with chiasmata, the physical manifestation of crossovers, holding homologous chromosomes together as a single bivalent unit (Fig. 1). During this lengthy dictyate arrest, which can last for months in mice or decades in humans, the chiasmata are maintained by cohesion between sister chromatids, particularly cohesion on the chromosome arms distal to the chiasmata [6,9].

Hormonal stimulation during the adult oestrus cycle subsequently induces groups of dictyate oocytes to grow, mature, and eventually resume meiotic prophase and progress into metaphase I. The bivalent chromosomes are held together by chiasmata and arm cohesion as they align on the meiotic spindle in metaphase I (Fig. 1) [6,11,12,14]. These physical links between homologous chromosomes, in combination with mono-orientation of sister centromeres, allow tension to be generated when centromeres from each homolog attach to opposite spindle poles. At least one chiasma is therefore required on each homologous chromosome pair to ensure balanced chromosome segregation in MI. As oocytes go through the metaphase I to anaphase I transition, sister chromatid cohesion on chromosome arms is released allowing chiasmata to resolve, and homologous chromosomes to segregate to opposite spindle poles. Sister chromatid cohesion at the centromeres is retained at this point and holds the two sister chromatids together (Fig. 1) [6,11,12,14]. As the oocytes progress into the MII, each pair of sister chromatids aligns on the metaphase II spindle with sister centromeres bi-oriented to opposite spindle poles. The oocyte then arrests at metaphase II and typically completes meiosis in response to fertilisation, removing centromeric cohesion to allow sister chromatids to separate and segregate to opposite spindle poles (Fig. 1) [6,11,12,14]. Both the meiotic divisions in oocytes are asymmetric, and extrude one set of chromosomes into small polar bodies that will degenerate during pre-implantation development, and retain one haploid set of chromosomes in the larger developmentally competent oocyte [6]. Generating and maintaining cohesion between sister chromatids and chiasmata between homologs during oocyte development are therefore key for preventing transmission of aneuploidies to the next generation.

3. Crossing over in foetal oocytes

3.1. Introduction to meiotic recombination

Meiotic recombination takes place during foetal stages of oocyte development, and is a key process in enabling the balanced metaphase I segregation of homologous chromosomes in adults. Recombination is initiated by the activity of the highly conserved endonuclease SPO11, which generates hundreds of DSBs across the genome during the start of meiotic prophase [13]. These DSBs subsequently recruit repair proteins which initiate a search for their homologous chromosome partner, promoting the pairing and synapsis of homologous chromosomes in mice [13]. The repair of meiotic DSBs to crossovers typically requires the heterodimeric complex of the mismatch repair proteins MLH1 and MLH3 [13]. These proteins can be visualised immunocytologically as foci localised to chromosomal axes in zygotene and pachytene foetal oocytes, and are interpreted as a reliable proxy for crossover frequency and positioning in both mouse and human germ cells [15,16]. The transient localisation of MLH1 in mouse and human oocytes, as well as the formation of ~10% of crossovers by an alternative pathway [15–17], make MLH1 foci counts conservative

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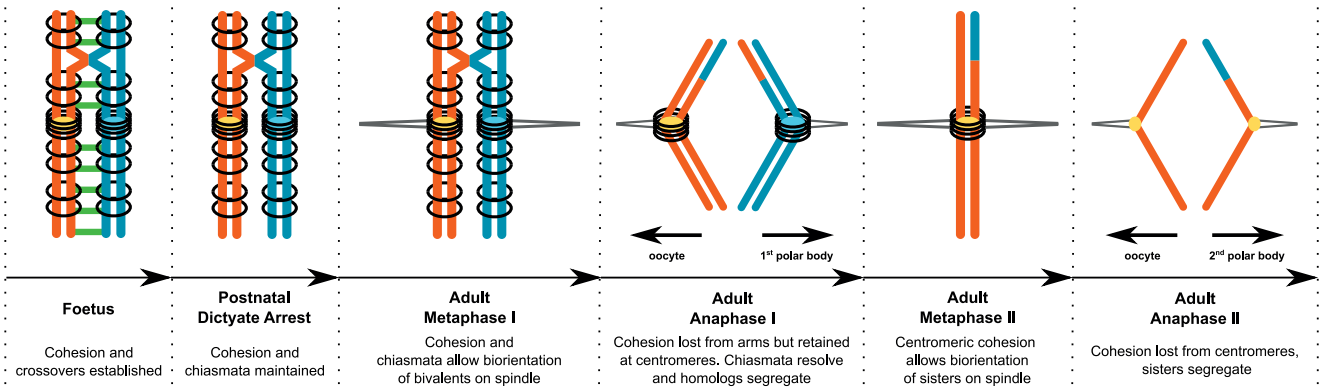

Fig. 1. Meiotic oocyte progression from foetus to adult. Schematic diagram showing how events that occur during foetal development influence meiosis I chromosome segregation in adult oocytes. Two homologous chromosomes (blue, orange), each comprising two sister chromatids, centromeres (light blue, light orange), sister chromatid cohesion (black circles), synaptonemal complex (green lines) and meiotic spindles (grey lines) are indicated. Sister chromatid cohesion and crossover exchanges/chiasmata established during foetal development provide a physical link between homologous chromosomes that persists after the synaptonemal complex disassembles and throughout dictyate. Chiasmata and sister chromatid cohesion facilitate bi-orientation of bivalent chromosomes on the meiotic spindle during metaphase I in adult oocytes. Removal of arm cohesion and resolution of chiasmata allows homologous chromosomes to segregate to opposite spindle poles in anaphase I, whilst centromeric cohesion continues to hold sister chromatids together at this stage. Removal of centromeric cohesion allows separation of sister chromatids in anaphase II. Both meiotic divisions are asymmetric and segregate one set of chromosomes into the oocyte, and the other into small polar bodies that degenerate during pre-implantation development.

estimates of crossover formation. As the synaptonemal complex dissociates, crossovers can be visualised as the chiasmata, though this is also a proxy for crossover formation as chiasmata are susceptible to migration or loss [6,9]. Whilst these cytological techniques are only applicable to analysis of recombination in MI germ cells, genotyping allows the crossover genetic exchanges occurring in foetal oocytes to be detected in subsequent stages of oocyte development and in adult offspring [5,18]. Genotyping relies on there being sufficient polymorphisms between the homologous chromosomes to identify the segments of chromosomes inherited together. Genotyping characteristic pericentromeric markers also enables identification of parental origin of surplus/absent chromosomes in aneuploidies and whether they are sister or homologous chromosomes [19,20].

3.2. Chromosomes without a crossover

As mammalian oocytes progress through the foetal stages of meiotic prophase it is essential that at least one crossover is formed by recombination between each pair of homologous chromosomes to ensure their balanced segregation during MI (Fig. 1, Fig. 2A). Genetic studies of Down's syndrome patients have estimated that ~30% of all maternally-derived cases with homologous chromosome segregation error have failed to form crossovers on the affected chromosome, indicating that this fault is often responsible for the resulting aneuploidy (Fig. 2B) [21]. Analysis of foetal oocytes has demonstrated that chromosomes 21 and 22 are the most common to lack MLH1-marked crossovers and do not have detectable MLH1 foci ~5% of the time [16]. The production line hypothesis proposed the formation of low numbers of crossovers in oocytes generated later in gestation, which would subsequently be ovulated later in adult life and predispose older mothers to aneuploidy [22]. However, MLH1 foci counts in oocytes of different gestational age indicates that no such drop in crossover formation exists [23]. Thus, the failure to form a crossover during foetal oocyte development contributes to oocyte aneuploidy independent of maternal age [21]. Low genome-wide recombination rates, rather than a specific reduction in crossovers on chromosome 21, are associated with Down's syndrome caused by a maternal failure to form a crossover on chromosome 21 [24]. Curiously, low genome-wide recombination rates are also seen in the siblings of these Down's syndrome patients, independent of maternal age, indicating that maternal factors influence the rate of crossover formation and the frequency at which chromosomes without a crossover arise during oogenesis [25].

3.3. Crossover frequency control

Crossover frequency as measured either by MLH1 foci counts or by genotyping is reported to vary ~10-fold in human oocytes both across the populations studied and within individuals [23,26,27]. The variation reported is much greater than that of human males and also mice of both sexes, indicating that the regulation of crossover frequency may be less strictly controlled in human females, potentially contributing to the high rate of maternally derived aneuploidies. Genome wide association studies to identify variants that influence maternal crossover frequency have led to the identification of a number of variants associated with this, including several in *RNF212* [28,29]. RNF212 is implicated in the control of recombination taking place in foetal oocytes, and has been demonstrated in mice to localise to meiotic recombination intermediates and promote their resolution by crossover formation [30]. Variants in this gene may be an example of a maternal factor accounting for low crossover rates in oocytes resulting in offspring with Down's syndrome or their healthy siblings.

Following the formation of several hundred DSBs in the foetal oocyte, some DSBs repair as non-crossovers or by inter-sister recombination and only ~10% of the original DSBs repair to form crossovers. Although many proteins are involved in DSB formation and homologous chromosome synapsis upstream of crossover formation, mutations or polymorphisms in these proteins typically cause defects in chromosome synapsis and infertility in mice [13] and these proteins may have limited effects on crossover frequency in human populations. A smaller group of proteins are implicated in promoting the repair of DSBs to form crossovers in mice, and these are good candidates for regulating crossover frequency in humans. The heterodimer of mismatch repair protein homologs MSH4 and MSH5 is essential for stabilising recombination intermediates and the formation of crossovers in mice [13]. MSH4 also physically associates with TEX11 during meiosis, a protein of unknown biochemical function that promotes crossover formation in mouse oocytes [31]. The stability of MSH4 and TEX11 at recombination intermediates in mice is controlled by the antagonistic relationship of the SUMO E3 ligase RNF212 [30] and the E3 ubiquitin ligase HEI10 [32]. The AAA+ ATPase TRIP13 is also involved in promoting crossover formation in mouse oocytes [33], though it is not

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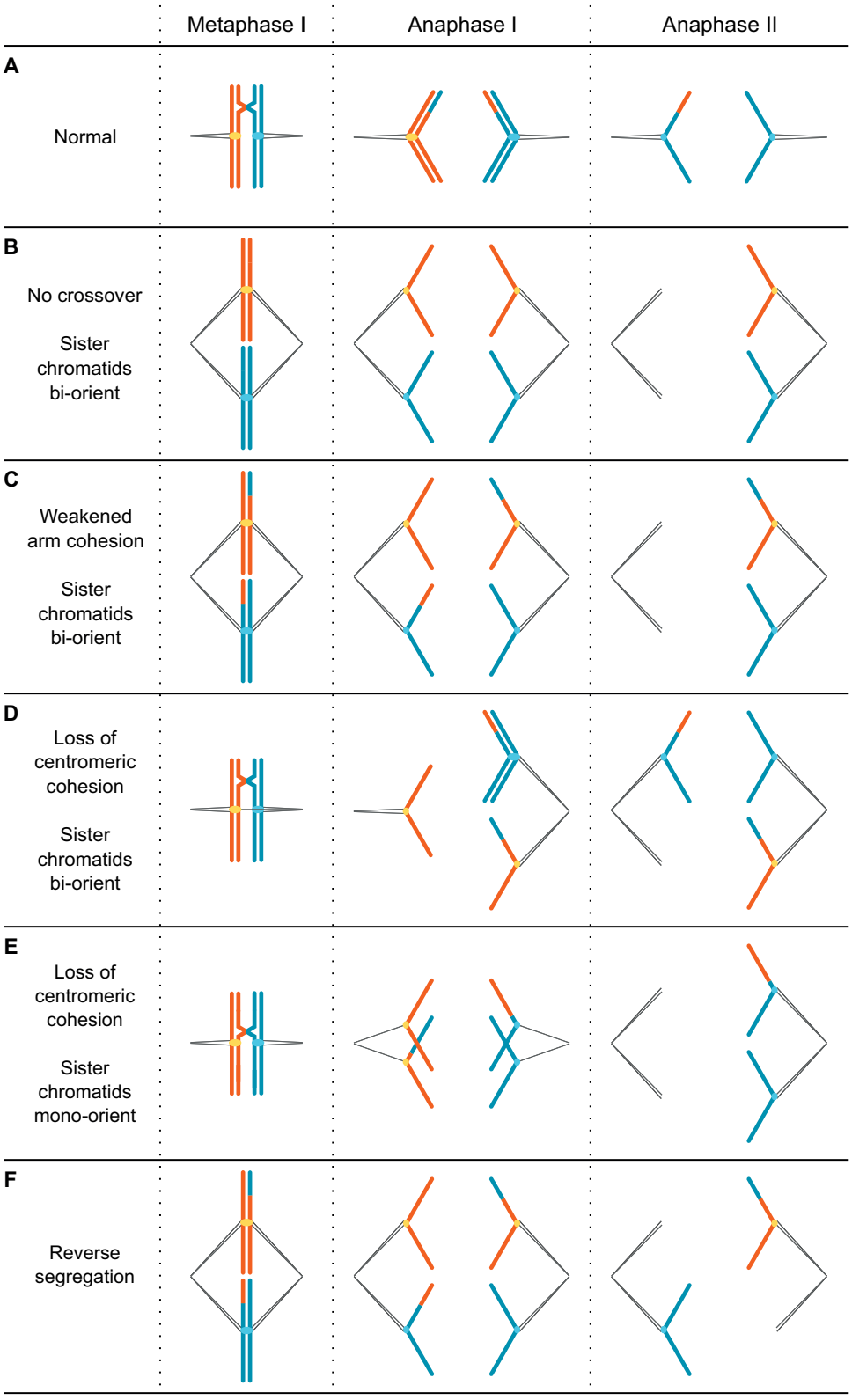

Fig. 2. Potential mechanisms contributing to chromosome missegregation in mammalian oocytes. Schematic diagram showing normal meiotic chromosome segregation (A), and some abnormal meiotic chromosome segregation patterns that can generate oocyte aneuploidy (B–E). Two homologous chromosomes (blue, orange), each comprising two sister chromatids, centromeres (light blue, light orange), and meiotic spindles (grey lines) are indicated. Failure to generate crossovers during foetal development (B), or loss of chiasmata caused by age-dependent weakening of arm cohesion (C), can cause missegregation due to bi-orientation of univalents on the MI spindle, and premature sister chromatid separation during MI. Age-dependent weakening of centromeric cohesion (D), possibly exacerbated by peri-centromeric crossovers (E), can cause missegregation due to bi-orientation of sister chromatids on the meiosis I spindle (D) and/or premature separation of sister chromatids during meiosis I (E). Weakening of centromeric cohesion could potentially affect one (D) or both (E) homologous chromosomes in the same division. A number of additional meiotic chromosome segregation errors are possible which, for clarity, are not depicted here. Any of the abnormal segregation patterns that involve bi-orientation of sister centromeres and premature segregation of sister chromatids at meiosis I can still generate normal haploid oocytes if homologous chromatids partition to different cells in meiosis II (F).

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yet clear how it relates to other components of the recombination machinery. *MSH4*, *MSH5*, *TEX11*, *HEI10*, *RNF212*, and *TRIP13* are therefore good candidates for regulators of maternal recombination in humans and potential risk factors for increased incidence of oocyte aneuploidy.

3.4. Susceptible exchanges

Maternally-derived Down's syndrome usually involves copies of chromosome 21 that have undergone a single detectable crossover exchange [21]. However, the position of these single crossovers along the chromosome can predispose it to missegregation. Single crossovers in regions close to the telomere rarely occur in human oocytes contributing to healthy conceptions, but are enriched in maternally-derived Down's syndrome trisomies caused by homolog missegregation [21]. Telomeric chiasmata are conceivably most sensitive to being lost from chromosome arms as there is less distal arm cohesion maintaining them. The incidence of Down's syndrome involving copies of chromosome 21 with telomeric crossovers is largely independent of maternal age, suggesting that some weakening of arm cohesion and loss of chiasmata occurs even in oocytes from young mothers. Similarly, single telomeric crossovers on chromosome 16 are thought to cause the high incidence of chromosome 16 univalents in oocytes of young mothers, and the high rates of trisomy associated with this chromosome [34,35]. However, as maternal age increases, copies of chromosome 21 that have crossovers positioned further from telomeres become more susceptible to missegregation, and missegregation is not restricted to those copies of chromosome 21 that have telomeric exchanges [21,36]. This is likely due to failed chiasmata maintenance caused by age-dependent weakening of sister chromatid cohesion (Fig. 2C, Section 4.4).

Remarkably, positioning of crossovers proximal to the centromere has been shown to leave chromosomes susceptible to sister chromatid missegregation in cases of maternally-derived Down's syndrome [19,20]. Peri-centromeric exchanges are risk factors for trisomy 21 even when this chromosome has two crossovers rather than one [37]. Contrary to telomeric exchanges, peri-centromeric crossovers are rarely observed in cases originating from younger mothers, but observed much more frequently with maternal age [21]. Therefore such cases fit with the proposed two-hit model of chromosome missegregation [20]. The first hit is formation of a susceptible crossover pattern during foetal development, and the second hit is the age-dependent increase in risk of that susceptible chromosome missegregating. It is possible that peri-centromeric crossovers disrupt centromeric cohesion between sister chromatids in MI, further compromising age-dependent weakening of cohesion (Fig. 2E), although there are other mechanistic interpretations of this genetic association [6,21]. In summary, particular recombination patterns established at foetal stages of oocyte development can predispose both homologous chromosomes and sister chromatids to missegregation during the meiotic divisions in adult oocytes.

3.5. Factors regulating crossover position

Crossover positioning is subject to regulation at multiple stages of meiotic recombination. For a crossover to form at a locus a DSB must first be generated to participate in recombination. DSB formation is enriched at certain hotspots throughout the genome [13], which are determined at least in part by the zinc-finger histone methyltransferase PRDM9 [13]. Research in human spermatocytes has demonstrated that crossover frequency in a particular position largely correlates with DSB frequency at that site [38], although analysis of specific hotspots in mice suggests that there can be significant regional and sex-specific differences in the proportion of DSBs that mature into crossovers at some sites [39]. Crossover formation at certain locations makes chromosomes susceptible to missegregation, therefore such defects could be traced back to positioning of DSBs at vulnerable loci.

The distribution of crossovers over the genome tends to follow a pattern with three potentially related features: (i) at least one crossover is typically formed between each pair of homologous chromosomes [15], (ii) crossover frequency is buffered from fluctuation in DSB frequency by a process of crossover homeostasis [40], and (iii) multiple crossovers are distributed across chromosomes by crossover interference inhibiting their formation in close proximity [12,15]. The mechanism(s) influencing this distribution are not known, though research in mice indicates that chromatin loop organisation influences crossover promotion [41], and work in yeast has led to a model where crossover formation is regulated by physical chromosomal stress in a pathway involving topoisomerase II [42]. The strength of crossover interference correlates with physical distance along the synaptonemal complex, thus this structure is thought to be involved in interference transmission [43]. Indeed, higher crossover frequency in human oocytes compared to spermatocytes correlates with differences in synaptonemal complex length [43,44]. Defects in mechanisms influencing this control of crossover distribution could generate chromosomes without a crossover that ultimately missegregate resulting in aneuploidy.

3.6. Chromosome missegregation in human oocytes

Genotyping Down's syndrome patients has demonstrated that around three-quarters of maternally-derived cases are caused by missegregation of homologous chromosomes, and a quarter by missegregation of sister chromatids [4,19]. This is consistent with a wealth of cytological data indicating that the most prevalent chromosome missegregation events in human oocytes from older women involve premature separation and segregation of sister chromatids during MI (Fig. 2C–E) [6]. A recent genetic study combining analysis of all three products of a complete female meiotic division: the first and second polar body, and the oocyte, has provided further insight into the mechanisms of chromosome missegregation in human oocytes [27]. This study revealed that even in cases where recombination took place between homologs, a failure to form multiple crossovers involving all four chromatids in exchanges predisposes to premature separation of an individual sister chromatid during MI [27]. However, the most common segregation error involved premature separation and segregation of sister chromatids from both homologs in MI (Fig. 2C), a conclusion similar to that reached from imaging and analysis of ageing mouse oocytes [45,46]. This MI segregation error occurs much more frequently than expected if each homolog in a bivalent lost cohesion independently (Fig. 2D), suggesting an alternative mechanism is involved [27]. Live imaging of young and old mouse oocytes has demonstrated that bivalents separate into univalents during metaphase I more frequently in older oocytes, then bi-orient on the MI spindle [47]. This results in premature separation and segregation of sister chromatids during MI, which could partition independently during MII to generate either an aneuploid oocyte (Fig. 2C), or a haploid oocyte with normal chromosome complement (Fig. 2F). A similar mechanism may be responsible for the common MI segregation errors reported in human oocytes [27]. The production of a normal haploid oocyte following premature segregation of sister chromatids in MI and correction by segregation of homologs in MII (Fig. 2F), a phenomenon described as "reverse segregation", was indeed found to frequently occur in humans [27]. Failure to form crossovers between homologs during foetal development presumably results in a similar pattern of chromosome missegregation (Fig. 2B) and potentially also reverse segregation. Generating and maintaining at least one chiasmata per homologous

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chromosome pair during foetal oocyte development, through the prolonged dictyate arrest and up to metaphase I therefore appears to be crucial for faithful meiotic chromosome segregation in the adult oocyte.

4. The role of cohesins in foetal and postnatal oocyte development

4.1. Cohesins in meiosis

The sister chromatid cohesion that will mediate meiotic chromosome segregation in adult oocytes is established during foetal development. Sister chromatid cohesion is generated by the cohesin complex which forms a tripartite ring like structure that holds sister chromatids together [48]. The cohesin complex comprises four subunits: a core V-shaped heterodimer of two SMC (Structural Maintenance of Chromosomes) subunits; a kleisin subunit which closes and stabilises the ring-like structure; and one SA (Stromalin Antigen) subunit that associates with the kleisin. In mitotic cells the two SMC subunits are SMC1α and SMC3, the kleisin subunit is RAD21, and the SA subunit is either SA1 or SA2. Meiotic cells express additional SMC and SA subunits named SMC1β and STAG3 respectively, and two additional kleisin subunits, REC8 and RAD21L [9,49].

The presence of multiple flavours of cohesin subunits in meiotic cells means that many different hypothetical cohesin complexes can be generated containing different combinations of alternative SMC1, kleisin and SA subunits. Immunoprecipitation of cohesin subunits from testes extracts reveal that SMC1α and SMC1β do exist in several different complexes with other cohesin subunits *in vivo* [50]. However, not all hypothetical cohesin complexes are detectable in meiotic cells, for example the meiotic SA subunit STAG3 is present in cohesin complexes with REC8 or RAD21L meiotic kleisins, but not with the mitotic kleisin RAD21 in mouse testes [51,52]. Interestingly, different flavours of the same cohesin subunit can localise to distinct regions of meiotic chromosomes in mouse oocytes and spermatocytes [51–54] suggesting that different cohesin complexes could have distinct functions in mammalian meiosis.

Cohesins can promote intra-molecular interactions between different regions of DNA on the same chromosome in addition to inter-molecular interactions between DNA on sister chromosomes [48]. The former may be important for generating loops of chromatin that are thought to underlie the structure of meiotic chromosomes [55], and some of the roles and localisations of meiotic cohesin subunits may reflect this aspect of cohesin function. Indeed, only some of the flavours of cohesin expressed in oocytes function in sister chromatid cohesion during the meiotic divisions. Sister chromatid cohesion in metaphase I mouse oocytes depends on an intact REC8 kleisin subunit suggesting that any cohesin complexes that contain the meiotic RAD21L or mitotic RAD21 kleisins are not sufficient to generate functional sister chromatid cohesion in these cells [56]. In contrast, some functional sister chromatid cohesion can be generated in meiotic oocytes lacking the meiotic SMC1β cohesin, presumably by cohesin complexes containing the mitotic SMC1α cohesin [57]. The ability of mitotic cohesins to function in sister chromatid cohesion in meiotic oocytes may be related to differences in the way that different cohesin subunits, and different flavours of cohesin subunit, are regulated.

4.2. Establishment of cohesion

Studies in yeast and mammalian mitotic cells have revealed that cohesin loading onto DNA during DNA replication requires the heterodimeric cohesin loading factor NIPBL-MAU2 [58,59]. Cohesin is loaded onto DNA through the opening of an entry gate at the interface of the SMC1 and SMC3 subunits. Once loaded, cohesin can be released from DNA by opening an exit gate at the interface of the SMC3 and kleisin subunits [58,59]. Loading cohesin onto chromatin is required but not sufficient for cohesion to be established between sister chromatids. During establishment of cohesion, acetylation of SMC3 by the acetyltransferase ECO1 leads to the recruitment of sororin which promotes sister chromatid cohesion by displacing WAPL from its interacting partner PDS5, and preventing WAPL-dependent removal of cohesin from the chromatin [58–61]. The recruitment of sororin therefore locks the loaded-cohesin complexes onto DNA and marks a sub-population of cohesin that is more tightly associated with chromatin [62]. It is not yet known whether SMC3 acetylation occurs during the establishment of sister chromatid cohesion in mammalian oocytes, or if sororin plays a role in protecting any acetylated SMC3-marked cohesin from WAPL-mediated dissociation. However, any genetic variation or environmental influences during human foetal development that alter the activity of the genes involved in the establishment of meiotic cohesion could potentially affect the incidence of aneuploidy in adult oocytes.

4.3. Cohesin removal

During mammalian mitosis, removal of cohesin occurs in two discrete steps [63]. Firstly, phosphorylation of cohesin and shugoshin by the prophase pathway allows WAPL to remove cohesin from chromosome arms by a non-proteolytic mechanism, whilst centromeric cohesin is protected by a complex of shugoshin and protein phosphatase 2A (SGO1-PP2A) [58,59,61]. In the second step of mitotic cohesin removal, activation of the anaphase promoting complex at the metaphase-anaphase transition stimulates the ubiquitylation and proteasome-dependent degradation of securin, an inhibitor of separase. Separase then removes centromeric cohesion by proteolytically cleaving the kleisin subunit, triggering anaphase and chromosome segregation [58,59].

In contrast to mitotic cells, removal of arm cohesin in meiosis requires separase-mediated proteolysis of REC8 [64]. It is unknown whether WAPL-mediated cohesin removal occurs in oocytes, however conditional knockdown of separase post-natally in growing oocytes prevents chiasmata resolution and polar body extrusion [64]. Therefore, whether a WAPL pathway operates or not, it is unable to compensate for separase-mediated cohesin removal at anaphase I. As in mitotic cells, shugoshin acts with PP2A in MI to protect centromeric cohesin from separase cleavage [65]. In yeast, SGO-PP2A appears to protect centromeric cohesion during MI by antagonising REC8 phosphorylation which is essential for its cleavage by separase [66], but whether this mechanism is conserved in mammalian oocytes is unknown [66]. Over-expression of SGO1 in mouse oocytes has been shown to block homologous chromosome segregation but only when it is capable of interacting with PP2A [67], thus demonstrating the essential interaction between these proteins.–Protection of centromeric cohesion in mouse oocytes is normally mediated by SGO2 shugoshin [65]. Mammalian SGO2 colocalises with centromeric REC8 at metaphase I, where it is stabilised by meikin, a meiosis-specific kinetochore protein that helps protect centromeric cohesion and prevents sister chromatids bi-orienting to opposite spindle poles at this stage [65,68]. SGO2 is redistributed at metaphase II by spindle-associated tension acting across the sister centromeres. This relocation of SGO2/PP2A is thought to permit removal of centromeric REC8 during metaphase II–anaphase II resulting in sister chromatid segregation [65,66]. Clearly, there are fundamental differences in the pathways used to remove arm cohesion in meiosis and mitosis, however some of the proteins involved in protection and cleavage of centromeric cohesin appear to be the same. As will become clear in Section 4.4,

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pathways that remove cohesin from meiotic chromosomes in resting dictyate oocytes may play a role in age-dependent aneuploidy in mammalian oocytes.

4.4. Cohesion decay in mice

The cohesion that is established in foetal oocytes needs to be maintained throughout the prolonged dictyate arrest to mediate faithful meiotic chromosome segregation in the adult oocytes. One of the first indications that defects in cohesins play a role in age-related aneuploidy came from studies of mice lacking the meiosis-specific SMC protein, SMC1β [57,69]. Despite having reduced cohesion at the early stages of chromosome condensation, *SMC1β*$^{-/-}$ oocytes progress through meiosis I to dictyate arrest. Whilst MLH1 foci are normally distributed in *SMC1β*$^{-/-}$ foetal oocytes, there is failure to maintain sister chromatid cohesion as chiasmata position is skewed in adult oocytes, with chiasmata being found in more terminal positions [57]. This reduction in cohesion and terminalisation of chiasmata results in fewer chiasmata, increased frequency of univalent chromosomes, and single chromatids, leading to-considerable aneuploidy and consequent sterility [69]. Importantly, comparison of chromosome preparations from one month and two month old mice revealed that the severity of these defects increased with age. Therefore, reduced levels of cohesion in *SMC1β*$^{-/-}$ post-natal oocytes accelerates the appearance of defects similar to those seen in naturally ageing mice.

Interestingly, conditional inactivation of *SMC1β* shortly after birth has no effect on sister chromatid cohesion, chiasma placement or fertility in female mice [70]. Similarly, elegant genetic experiments in mice that conditionally express *REC8* at different stages of oogenesis demonstrate that *REC8* expression post-natally in growing oocytes is not able to function in sister chromatid cohesion during meiosis I [56]. This suggests that cohesion which is lost or removed from oocytes post-natally is not replaced, and that the meiotic cohesins that are loaded onto DNA in foetal life must be maintained in adults.

Different strains of naturally aged mice have a marked reduction in the amount of the meiotic kleisin REC8 on chromosome arms and centromeres in metaphase I oocytes and SMC1β, is similarly reported to be markedly reduced in older oocytes [45,46,71]. This age related decrease in REC8 and SMC1β abundance has also been observed in dictyate mouse oocytes suggesting that this deterioration occurs during dictyate arrest [72]. Whether or not the observed changes in REC8 and SMC1β abundance reflect the behaviour of the entire cohesin complex is unknown, but, consistent with an age-dependent loss of cohesion at centromeres, the distance between sister kinetochores is larger in older oocytes [45,46]. Older oocytes are also less able to maintain chiasmata and have an increased proportion of prometaphase I chromosomes with either a single chiasma located distally on the bivalent, or with no visible chiasmata between univalents that are loosely associated at their telomeres [22,45,46,73]. Migration, terminalisation and loss of chiasmata in older oocytes could potentially reflect weakened sister chromatid cohesion on chromosome arms, particularly cohesion distal to the chiasmata [9]. Therefore, the age-dependent depletion of cohesin from meiotic chromosomes in oocytes appears to be associated with weakening of cohesion along chromosome arms and at centromeres.

The number of single chromatids in old oocytes at metaphase II is much higher than the number of unpaired univalents in prometaphase I suggesting that the primary chromosome segregation error in ageing mouse oocytes involves premature separation of sister chromatids [45,46]. Weakening of centromeric cohesion would allow sister chromatids to either erroneously bi-orient during metaphase I then prematurely separate and segregate at anaphase I (Fig. 2D), or to prematurely separate in anaphase I after correctly mono-orienting in metaphase I (Fig. 2E). Although a spindle assembly checkpoint operates effectively in young and old oocytes to monitor attachment of chromosomes to the meiosis I spindle, bi-orientation of sister chromatids during meiosis I is not detected by this checkpoint [6,45,46,74]. However, weakening of arm cohesion may play a role in the premature separation of sister chromatids in ageing mouse oocytes as live imaging suggests that bi-orientation and premature separation of sister chromatids on the meiosis I spindle may be preceded by bivalent chromosomes prematurely resolving into transient univalents during metaphase I (Fig. 2C) [47]. The loss of cohesion from meiotic chromosomes in oocytes from older mice could therefore potentially account for at least some of the chromosome missegregation and aneuploidy associated with maternal ageing.

In oocytes, sister chromatids are normally prevented from separating prematurely during metaphase I–anaphase I by SGO2 [65], and loss of chromosome cohesion in aged oocytes correlates with reduced levels of SGO2 on meiotic chromosomes during both MI and MII [46,73]. Interestingly, SGO2 has also been found to localise to chromosome arms, as well as centromeres in metaphase I oocytes, suggesting that SGO2 may also play a role in protecting arm cohesin in meiosis I before the onset of anaphase [46]. The levels of both arm and centromeric associated SGO2 are also reduced in *SMC1β*$^{-/-}$ oocytes, suggesting that cohesin depletion during prolonged dictyate arrest results in reduced recruitment of SGO2, which may in turn amplify loss of cohesion as oocytes age [46].

4.5. Cohesion decay in humans

Similar to the findings from naturally aged mice, immunofluorescent staining of human oocytes in ovarian sections has shown that the level of meiosis-specific cohesins, REC8 and SMC1β are decreased in dictyate oocytes in small follicles from older women [72]. Whether or not there is a reduction in arm cohesin, centromeric cohesin or both in the human oocytes is unclear. Consistent with a reduction in cohesin however, inter-kinetochore distances increase significantly and chromosome segregation errors occur more frequently in human eggs with advanced age [47,75]. Cohesin levels and loss of cohesion shows a linear negative correlation with oocyte age [72] however, the frequency of chromosome segregation errors rises exponentially in women in their mid-thirties [4]. Consistent with the findings in naturally aged mice [45], it seems that a threshold level of cohesin is also required in human oocytes in order to prevent missegregation [72]. Interestingly, aside from the age-effect, the rate of cohesion decrease varied between individuals which could indicate that genetic or environmental variation between individuals could be influencing susceptibility to age-dependent oocyte aneuploidy [72]. Clearly, studies from both human and mouse oocytes suggest that loss of chromosome-associated cohesins leads to weakening of cohesion and meiotic errors. However, further research is required to establish if cohesins are being removed from chromosomes during oocyte ageing by one of the known pathways for cohesin removal, by non-specific processes, such as oxidative damage or spontaneous hydrolysis of peptides bonds, or by as yet unidentified mechanisms.

5. Conclusions

It is becoming clear that the developmental strategy used by mammalian oocytes plays a significant part in the high rates of age-dependent maternal aneuploidy seen in humans. Events that occur in foetal oocytes such as failure to form a crossover, or crossover formation in a susceptible location, can lead to chromosome segregation errors and aneuploidy in adult oocytes. As maternal

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age increases, maintaining chiasmata and sister chromatid cohesion becomes more of an issue and mechanisms that promote loss of these in post-natal oocytes have a stronger influence on the incidence of oocyte aneuploidy. Huge progress has been made in recent years in our molecular understanding of how sister chromatid cohesion is established, generated and removed during meiosis, and in deciphering the chromosome segregation defects that contribute to aneuploidy in ageing oocytes. Understanding the primary mechanisms contributing to loss of sister chromatid cohesion in post-natal oocytes would seem to be the next major question that needs to be answered, and is one that will be key if any therapeutic interventions to slow chromosomal ageing in human oocytes are to be developed in the future.

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References

[1] Jacobs PA, Strong JA. A case of human intersexuality having a possible XXY sex-determining mechanism. Nature 1959;183:302–3.
[2] Lejeune J, Gauthier M, Turpin R. Les chromosomes humains en culture de tissus. C. R. Hebd. Seances Acad. Sci 1959;248:602–3.
[3] Jacobs PA, Baikie AG, Court Brown WM, Strong JA. The somatic chromosomes in mongolism. Lancet 1959;1:710.
[4] Hassold T, Hunt P. To err (meiotically) is human: the genesis of human aneuploidy. Nat. Rev. Genet 2001;2:280–91, http://dx.doi.org/10.1038/35066065.
[5] Nagaoka SI, Hassold TJ, Hunt PA. Human aneuploidy: mechanisms and new insights into an age-old problem. Nat. Rev. Genet 2012;13:493–504, http://dx.doi.org/10.1038/nrg3245.
[6] Herbert M, Kalleas D, Cooney D, Lamb M, Lister L. Meiosis and maternal aging: insights from aneuploid oocytes and trisomy births. Cold Spring Harb. Perspect. Biol 2015;7:a017970, http://dx.doi.org/10.1101/cshperspect.a017970.
[7] McLaren A. Primordial germ cells in the mouse. Dev. Biol 2003;262:1–15.
[8] Kocer A, Reichmann J, Best D, Adams IR. Germ cell sex determination in mammals. Mol. Hum. Reprod 2009;15:205–13, http://dx.doi.org/10.1093/molehr/gap008.
[9] Jessberger R. Age-related aneuploidy through cohesion exhaustion. EMBO Rep 2012;13:539–46, http://dx.doi.org/10.1038/embor.2012.54.
[10] Öllinger R, Reichmann J, Adams IR. Meiosis and retrotransposon silencing during germ cell development in mice. Differentiation 2010;79:147–58, http://dx.doi.org/10.1016/j.diff.2009.10.004.
[11] Page SL, Hawley RS. Chromosome choreography: the meiotic ballet. Science 2003;301:785–9, http://dx.doi.org/10.1126/science.1086605.
[12] Petronczki M, Siomos MF, Nasmyth K. Un ménage à quatre: the molecular biology of chromosome segregation in meiosis. Cell 2003;112:423–40.
[13] Baudat F, Imai Y, de Massy B. Meiotic recombination in mammals: localization and regulation. Nat. Rev. Genet 2013;14:794–806, http://dx.doi.org/10.1038/nrg3573.
[14] Hauf S, Watanabe Y. Kinetochore orientation in mitosis and meiosis. Cell 2004;119:317–27, http://dx.doi.org/10.1016/j.cell.2004.10.014.
[15] Anderson LK, Reeves A, Webb LM, Ashley T. Distribution of crossing over on mouse synaptonemal complexes using immunofluorescent localization of MLH1 protein. Genetics 1999;151:1569–79.
[16] Cheng EY, Hunt PA, Naluai-Cecchini TA, Fligner CL, Fujimoto VY, Pasternack TL, et al. Meiotic recombination in human oocytes. PLoS Genet 2009;5:e1000661, http://dx.doi.org/10.1371/journal.pgen.1000661.
[17] Holloway JK, Booth J, Edelmann W, McGowan CH, Cohen PE. MUS81 generates a subset of MLH1-MLH3-independent crossovers in mammalian meiosis. PLoS Genet 2008;4:e1000186, http://dx.doi.org/10.1371/journal.pgen.1000186.
[18] Hou Y, Fan W, Yan L, Li R, Lian Y, Huang J, et al. Genome analyses of single human oocytes. Cell 2013;155:1492–506, http://dx.doi.org/10.1016/j.cell.2013.11.040.
[19] Lamb NE, Feingold E, Savage A, Avramopoulos D, Freeman S, Gu Y, et al. Characterization of susceptible chiasma configurations that increase the risk for maternal nondisjunction of chromosome 21. Hum. Mol. Genet 1997;6:1391–9.
[20] Lamb NE, Freeman SB, Savage-Austin A, Pettay D, Taft L, Hersey J, et al. Susceptible chiasmate configurations of chromosome 21 predispose to non-disjunction in both maternal meiosis I and meiosis II. Nat. Genet 1996;14:400–5, http://dx.doi.org/10.1038/ng1296-400.
[21] Oliver TR, Feingold E, Yu K, Cheung V, Tinker S, Yadav-Shah M, et al. New insights into human nondisjunction of chromosome 21 in oocytes. PLoS Genet 2008;4:e1000033, http://dx.doi.org/10.1371/journal.pgen.1000033.
[22] Henderson SA, Edwards RG. Chiasma frequency and maternal age in mammals. Nature 1968;218:22–8.
[23] Rowsey R, Gruhn J, Broman KW, Hunt PA, Hassold T. Examining variation in recombination levels in the human female: a test of the production-line hypothesis. Am. J. Hum. Genet 2014;95:108–12, http://dx.doi.org/10.1016/j.ajhg.2014.06.008.
[24] Brown AS, Feingold E, Broman KW, Sherman SL. Genome-wide variation in recombination in female meiosis: a risk factor for non-disjunction of chromosome 21. Hum. Mol. Genet 2000;9:515–23.
[25] Middlebrooks CD, Mukhopadhyay N, Tinker SW, Allen EG, Bean LJH, Begum F, et al. Evidence for dysregulation of genome-wide recombination in oocytes with nondisjoined chromosomes 21. Hum. Mol. Genet 2014;23:408–17, http://dx.doi.org/10.1093/hmg/ddt433.
[26] Lenzi ML, Smith J, Snowden T, Kim M, Fishel R, Poulos BK, et al. Extreme heterogeneity in the molecular events leading to the establishment of chiasmata during meiosis I in human oocytes. Am. J. Hum. Genet 2005;76:112–27, http://dx.doi.org/10.1086/427268.
[27] Ottolini CS, Newnham LJ, Capalbo A, Natesan SA, Joshi HA, Cimadomo D, et al. Genome-wide maps of recombination and chromosome segregation in human oocytes and embryos show selection for maternal recombination rates. Nat. Genet 2015;47:727–35, http://dx.doi.org/10.1038/ng.3306.
[28] Chowdhury R, Bois PRJ, Feingold E, Sherman SL, Cheung VG. Genetic analysis of variation in human meiotic recombination. PLoS Genet 2009;5:e1000648, http://dx.doi.org/10.1371/journal.pgen.1000648.
[29] Kong A, Thorleifsson G, Stefansson H, Masson G, Helgason A, Gudbjartsson DF, et al. Sequence variants in the RNF212 gene associate with genome-wide recombination rate. Science 2008;319:1398–401, http://dx.doi.org/10.1126/science.1152422.
[30] Reynolds A, Qiao H, Yang Y, Chen JK, Jackson N, Biswas K, et al. RNF212 is a dosage-sensitive regulator of crossing-over during mammalian meiosis. Nat. Genet 2013;45:269–78, http://dx.doi.org/10.1038/ng.2541.
[31] Yang F, Gell K, van der Heijden GW, Eckardt S, Leu NA, Page DC, et al. Meiotic failure in male mice lacking an X-linked factor. Genes Dev 2008;22:682–91, http://dx.doi.org/10.1101/gad.1613608.
[32] Qiao H, Prasada Rao HBD, Yang Y, Fong JH, Cloutier JM, Deacon DC, et al. Antagonistic roles of ubiquitin ligase HEI10 and SUMO ligase RNF212 regulate meiotic recombination. Nat. Genet 2014;46:194–9, http://dx.doi.org/10.1038/ng.2858.
[33] Roig I, Dowdle JA, Toth A, de Rooij DG, Jasin M, Keeney S. Mouse TRIP13/PCH2 is required for recombination and normal higher-order chromosome structure during meiosis. PLoS Genet 2010;6, http://dx.doi.org/10.1371/journal.pgen.1001062.
[34] Garcia-Cruz R, Casanovas A, Brieño-Enríquez M, Robles P, Roig I, Pujol A, et al. Cytogenetic analyses of human oocytes provide new data on non-disjunction mechanisms and the origin of trisomy 16. Hum. Reprod 2010;25:179–91, http://dx.doi.org/10.1093/humrep/dep347.
[35] Hassold T, Merrill M, Adkins K, Freeman S, Sherman S. Recombination and maternal age-dependent nondisjunction: molecular studies of trisomy 16. Am. J. Hum. Genet 1995;57:867–74.
[36] Lamb NE, Yu K, Shaffer J, Feingold E, Sherman SL. Association between maternal age and meiotic recombination for trisomy 21. Am. J. Hum. Genet 2005;76:91–9, http://dx.doi.org/10.1086/427266.
[37] Oliver TR, Tinker SW, Allen EG, Hollis N, Locke AE, Bean LJH, et al. Altered patterns of multiple recombinant events are associated with nondisjunction of chromosome 21. Hum. Genet 2012;131:1039–46, http://dx.doi.org/10.1007/s00439-011-1121-7.
[38] Pratto F, Brick K, Khil P, Smagulova F, Petukhova GV, Camerini-Otero RD. Recombination initiation maps of individual human genomes. Science 2014;346:1256442, http://dx.doi.org/10.1126/science.1256442.
[39] de Boer E, Jasin M, Keeney S. Local and sex-specific biases in crossover vs. noncrossover outcomes at meiotic recombination hot spots in mice. Genes Dev 2015;29:1721–33, http://dx.doi.org/10.1101/gad.265561.115.
[40] Cole F, Kauppi L, Lange J, Roig I, Wang R, Keeney S, et al. Homeostatic control of recombination is implemented progressively in mouse meiosis. Nat. Cell Biol 2012;14:424–30, http://dx.doi.org/10.1038/ncb2451.
[41] Kauppi L, Barchi M, Baudat F, Romanienko PJ, Keeney S, Jasin M. Distinct properties of the XY pseudoautosomal region crucial for male meiosis. Science 2011;331:916–20, http://dx.doi.org/10.1126/science.1195774.
[42] Zhang L, Wang S, Yin S, Hong S, Kim KP, Kleckner N. Topoisomerase II mediates meiotic crossover interference. Nature 2014;511:551–6, http://dx.doi.org/10.1038/nature13442.
[43] Petkov PM, Broman KW, Szatkiewicz JP, Paigen K. Crossover interference underlies sex differences in recombination rates. Trends Genet 2007;23:539–42, http://dx.doi.org/10.1016/j.tig.2007.08.015.
[44] Tease C, Hultén MA. Inter-sex variation in synaptonemal complex lengths largely determine the different recombination rates in male and female germ cells. Cytogenet. Genome Res 2004;107:208–15, http://dx.doi.org/10.1159/000080599.

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[45] Chiang T, Duncan FE, Schindler K, Schultz RM, Lampson MA. Evidence that weakened centromere cohesion is a leading cause of age-related aneuploidy in oocytes. Curr. Biol 2010;20:1522–8, http://dx.doi.org/10.1016/j.cub.2010.06.069.
[46] Lister LM, Kouznetsova A, Hyslop LA, Kalleas D, Pace SL, Barel JC, et al. Age-related meiotic segregation errors in mammalian oocytes are preceded by depletion of cohesin and Sgo2. Curr. Biol 2010;20:1511–21, http://dx.doi.org/10.1016/j.cub.2010.08.023.
[47] Sakakibara Y, Hashimoto S, Nakaoka Y, Kouznetsova A, Höög C, Kitajima TS. Bivalent separation into univalents precedes age-related meiosis I errors in oocytes. Nat. Commun 2015;6:7550, http://dx.doi.org/10.1038/ncomms8550.
[48] Nasmyth K, Haering CH. Cohesin: its roles and mechanisms. Annu. Rev. Genet 2009;43:525–58, http://dx.doi.org/10.1146/annurev-genet-102108-134233.
[49] McNicoll F, Stevense M, Jessberger R. Cohesin in gametogenesis. Curr. Top. Dev. Biol 2013;102:1–34, http://dx.doi.org/10.1016/B978-0-12-416024-8.00001-5.
[50] Jessberger R. Cohesin complexes get more complex: the novel kleisin RAD21L. Cell Cycle 2011;10:2053–4.
[51] Fukuda T, Fukuda N, Agostinho A, Hernández-Hernández A, Kouznetsova A, Höög C. STAG3-mediated stabilization of REC8 cohesin complexes promotes chromosome synapsis during meiosis. EMBO J 2014;33:1243–55, http://dx.doi.org/10.1002/embj.201387329.
[52] Hopkins J, Hwang G, Jacob J, Sapp N, Bedigian R, Oka K, et al. Meiosis-specific cohesin component, Stag3 is essential for maintaining centromere chromatid cohesion, and required for DNA repair and synapsis between homologous chromosomes. PLoS Genet 2014;10:e1004413, http://dx.doi.org/10.1371/journal.pgen.1004413.
[53] Biswas U, Wetzker C, Lange J, Christodoulou EG, Seifert M, Beyer A, et al. Meiotic cohesin SMC1β provides prophase I centromeric cohesion and is required for multiple synapsis-associated functions. PLoS Genet 2013;9:e1003985, http://dx.doi.org/10.1371/journal.pgen.1003985.
[54] Ishiguro K, Kim J, Fujiyama-Nakamura S, Kato S, Watanabe Y. A new meiosis-specific cohesin complex implicated in the cohesin code for homologous pairing. EMBO Rep 2011;12:267–75, http://dx.doi.org/10.1038/embor.2011.2.
[55] Borde V, de Massy B. Programmed induction of DNA double strand breaks during meiosis: setting up communication between DNA and the chromosome structure. Curr. Opin. Genet. Dev 2013;23:147–55, http://dx.doi.org/10.1016/j.gde.2012.12.002.
[56] Tachibana-Konwalski K, Godwin J, van der Weyden L, Champion L, Kudo NR, Adams DJ, et al. Rec8-containing cohesin maintains bivalents without turnover during the growing phase of mouse oocytes. Genes Dev 2010;24:2505–16, http://dx.doi.org/10.1101/gad.605910.
[57] Hodges CA, Revenkova E, Jessberger R, Hassold TJ, Hunt PA. SMC1beta-deficient female mice provide evidence that cohesins are a missing link in age-related nondisjunction. Nat. Genet 2005;37:1351–5, http://dx.doi.org/10.1038/ng1672.
[58] Nasmyth K. Cohesin: a catenase with separate entry and exit gates? Nat. Cell Biol 2011;13:1170–7, http://dx.doi.org/10.1038/ncb2349.
[59] Haarhuis JHI, Elbatsh AMO, Rowland BD. Cohesin and its regulation: on the logic of X-shaped chromosomes. Dev. Cell 2014;31:7–18, http://dx.doi.org/10.1016/j.devcel.2014.09.010.
[60] Nishiyama T, Ladurner R, Schmitz J, Kreidl E, Schleiffer A, Bhaskara V, et al. Sororin mediates sister chromatid cohesion by antagonizing Wapl. Cell 2010;143:737–49, http://dx.doi.org/10.1016/j.cell.2010.10.031.
[61] Tedeschi A, Wutz G, Huet S, Jaritz M, Wuensche A, Schirghuber E, et al. Wapl is an essential regulator of chromatin structure and chromosome segregation. Nature 2013;501:564–8, http://dx.doi.org/10.1038/nature12471.
[62] Schmitz J, Watrin E, Lénárt P, Mechtler K, Peters J-M. Sororin is required for stable binding of cohesin to chromatin and for sister chromatid cohesion in interphase. Curr. Biol 2007;17:630–6, http://dx.doi.org/10.1016/j.cub.2007.02.029.
[63] Waizenegger IC, Hauf S, Meinke A, Peters JM. Two distinct pathways remove mammalian cohesin from chromosome arms in prophase and from centromeres in anaphase. Cell 2000;103:399–410.
[64] Kudo NR, Wassmann K, Anger M, Schuh M, Wirth KG, Xu H, et al. Resolution of chiasmata in oocytes requires separase-mediated proteolysis. Cell 2006;126:135–46, http://dx.doi.org/10.1016/j.cell.2006.05.033.
[65] Lee J, Kitajima TS, Tanno Y, Yoshida K, Morita T, Miyano T, et al. Unified mode of centromeric protection by shugoshin in mammalian oocytes and somatic cells. Nat. Cell Biol 2008;10:42–52, http://dx.doi.org/10.1038/ncb1667.
[66] Wassmann K. Sister chromatid segregation in meiosis II: deprotection through phosphorylation. Cell Cycle 2013;12:1352–9, http://dx.doi.org/10.4161/cc.24600.
[67] Xu Z, Cetin B, Anger M, Cho US, Helmhart W, Nasmyth K, et al. Structure and function of the PP2A–shugoshin interaction. Mol. Cell 2009;35:426–41, http://dx.doi.org/10.1016/j.molcel.2009.06.031.
[68] Kim J, Ishiguro K, Nambu A, Akiyoshi B, Yokobayashi S, Kagami A, et al. Meikin is a conserved regulator of meiosis-I-specific kinetochore function. Nature 2015;517:466–71, http://dx.doi.org/10.1038/nature14097.
[69] Revenkova E, Eijpe M, Heyting C, Hodges CA, Hunt PA, Liebe B, et al. Cohesin SMC1 beta is required for meiotic chromosome dynamics, sister chromatid cohesion and DNA recombination. Nat. Cell Biol 2004;6:555–62, http://dx.doi.org/10.1038/ncb1135.
[70] Revenkova E, Herrmann K, Adelfalk C, Jessberger R. Oocyte cohesin expression restricted to predictyate stages provides full fertility and prevents aneuploidy. Curr. Biol 2010;20:1529–33, http://dx.doi.org/10.1016/j.cub.2010.08.024.
[71] Liu L, Keefe DL. Defective cohesin is associated with age-dependent misaligned chromosomes in oocytes. Reprod. Biomed. Online 2008;16:103–12.
[72] Tsutsumi M, Fujiwara R, Nishizawa H, Ito M, Kogo H, Inagaki H, et al. Age-related decrease of meiotic cohesins in human oocytes. PLOS ONE 2014;9:e96710, http://dx.doi.org/10.1371/journal.pone.0096710.
[73] Yun Y, Lane SIR, Jones KT. Premature dyad separation in meiosis II is the major segregation error with maternal age in mouse oocytes. Development 2014;141:199–208, http://dx.doi.org/10.1242/dev.100206.
[74] Duncan FE, Chiang T, Schultz RM, Lampson MA. Evidence that a defective spindle assembly checkpoint is not the primary cause of maternal age-associated aneuploidy in mouse eggs. Biol. Reprod 2009;81:768–76, http://dx.doi.org/10.1095/biolreprod.109.077909.
[75] Duncan FE, Hornick JE, Lampson MA, Schultz RM, Shea LD, Woodruff TK. Chromosome cohesion decreases in human eggs with advanced maternal age. Aging Cell 2012;11:1121–4, http://dx.doi.org/10.1111/j.1474-9726.2012.00866.x.

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