COMMENTARY

Oocyte aneuploidy–more tools to tackle an old problem

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Meiosis generates a single-copy genome during two successive rounds of cell division after a single round of DNA replication. Failure to transmit exactly one copy of each chromosome during fertilization gives rise to aneuploid embryos resulting in infertility and congenital abnormalities such as Down's syndrome. Aneuploidy attributable to meiotic errors is overwhelming due to chromosome segregation errors during female meiosis, and the incidence of these increases dramatically as women get older (1, 2). Because the oocyte is the only viable product of female meiosis, our understanding of predisposing events in human oocytes relies largely on inferences from genetic studies in cases of trisomy and on analysis of oocytes obtained from in vitro fertilization clinics. Progress toward understanding the underlying mechanisms has been hampered by a paucity of information on the outcome of both meiotic divisions. In PNAS, Tyc et al. (3) apply a mathematical framework to investigate the contribution of various pathways to oocyte aneuploidy using a large dataset of karyotypes obtained from human blastocysts.

Mammalian meiosis, like that of most organisms, involves reciprocal exchange of DNA between parental homologs. This occurs after premeiotic DNA replication and results in the formation of bivalent chromosomes (4). Bivalents consist of four chromatids linked at the sites of reciprocal DNA exchange (cross-overs) and stabilized by cohesion between sister chromatid arms. Cohesion is mediated by meiosis-specific cohesin complexes containing the alpha-kleisin subunit Rec8 (Fig. 1). Sequential removal of arm and centromeric cohesin by separase during two successive meiotic divisions resolves bivalent chromosomes to their four constituent chromatids. Loss of arm cohesin during anaphase I converts bivalents to dyad chromosomes consisting of a pair of chromatids linked by cohesin between sister centromeres (2, 5). Orderly segregation during meiosis I requires monoorientation of sister centromere pairs, such that they cosegregate during anaphase I. This results in a reductional division (6). After the transition from meiosis I to meiosis II, centromeric cohesin enables sister centromeres to biorient on the meiosis II spindle (2, 5). Upon cleavage of centromeric cohesin, dyads are converted to single chromatids, which segregate equationally to opposite poles of the meiosis II spindle. Protection of a centromeric cohesin by Shugoshin proteins (SGOL2 in mammals) until the onset of anaphase II is essential for orderly segregation of chromatids (7, 8). In oocytes, both meiotic divisions are highly asymmetrical, giving rise to two small nonviable polar bodies (Fig. 1).

Consistent with previous studies (9), Tyc et al. (3) found that only a tiny fraction (<1%) of meiotic errors are of paternal origin. Compared with males, the establishment and maintenance of bivalent chromosomes are compromised in female meiosis. In females, there is a greater risk of homologs failing to form cross-overs, or of forming them in precarious positions that are susceptible to premature resolution (10). Both result in segregation of unpaired homologs during meiosis I and have been identified as a major risk factor for trisomy 21 (1, 11). In stark contrast to males, who produce sperm on an ongoing basis from puberty, females are born with their lifetime supply of oocytes (9). Bivalents formed in utero are not resolved until shortly before ovulation. The ovulated egg remains arrested at metaphase of meiosis II until fertilization (2, 12) (Fig. 1). Thus, in humans, decades can elapse between the establishment of a bivalent chromosome and its resolution to a single-copy genome. Studies in mice indicate that progressive depletion of oocyte chromosomal cohesin during female aging is associated with deterioration of the bivalent chromosome architecture (2, 13), which may explain the marked age-related increase in oocyte aneuploidy. In addition, cohesin depletion at centromeres is likely to be amplified by reduced recruitment of its protector SGOL2 (2).

Taking account of a broad range of possible meiotic outcomes, Tyc et al. (3) developed three mathematical models to quantify the probability of different segregation patterns contributing to oocyte aneuploidy in both divisions. The models were tested using a previously published (14) clinical dataset

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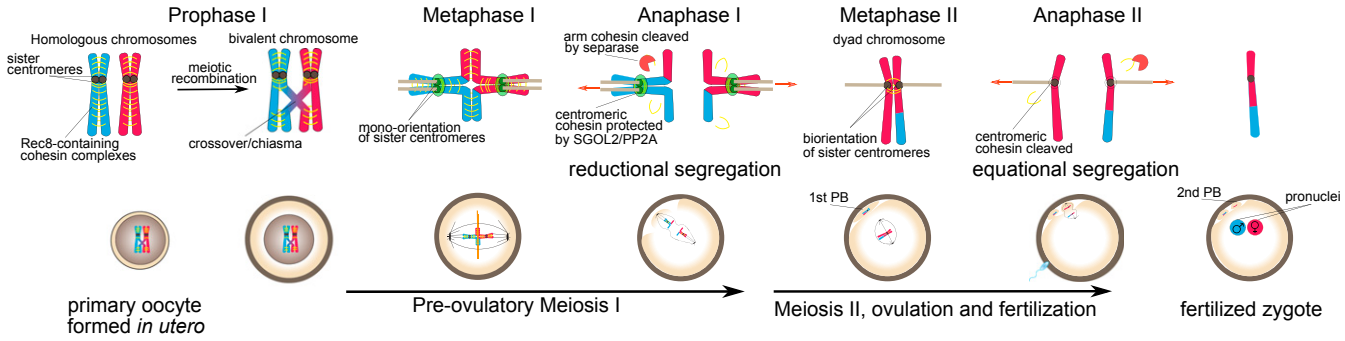

Fig. 1. Chromosome segregation during female meiosis. Meiotic recombination occurs in utero, giving rise to bivalent chromosomes. Bivalents are stabilized by cohesin on arms of sister chromatids. Removal of arm cohesin by separase during anaphase I converts bivalents to dyad chromosomes. The reductional division of meiosis I depends on monoorientation of sister centromeres. Centromeric cohesin is protected by SGOL2/PP2A to enable biorientation and equational segregation of chromatids during anaphase II. Eggs are ovulated after completion of meiosis I and remain arrested at metaphase II until sperm entry triggers completion of meiosis II. PB, polar body.

consisting of next-generation sequencing-derived karyotypes of trophectoderm biopsies obtained from day 5 blastocysts. After exclusion of putative sperm-derived meiotic errors and aneuploidy of mitotic origin, the dataset consisted of 11,157 blastocyst samples from 2,920 patients. Female age ranged from 20 to 48 y, and aneuploidy was detected in 35.3% of samples. The best-fit model proposed that the probability of missegregation during anaphase of meiosis II is influenced by the outcome of meiosis I. This model captured several previously established features of aneuploidy in human oocytes. Notably, the modeling results Tyc et al. (3) present support a marked effect of female age on the frequency of meiotic errors and on the number of chromosomes affected. Consistent with previous findings (2), they found that the probability of meiosis I errors attributable to premature loss of centromeric cohesion exceeded that of missegregation of intact dyads (meiosis I nondisjunction). The best-fit model did not distinguish between the two types of meiosis I defects but inferred that both contribute to an increased probability of missegregation during meiosis II, and this effect was amplified from the age of 38 y (3).

How do errors in meiosis I predispose to errors in meiosis II? Meiosis I nondisjunction refers to failure of homologous chromosomes to segregate to opposite spindle poles. This is primarily thought to be due to segregation of unpaired homologs. The segregation pattern of unpaired homologs during meiosis I largely determines the outcome of the meiosis II division. In the event that both sets of sister centromeres remain intact and cosegregate to the same spindle pole, the outcome of the meiosis II division will almost inevitably be aneuploid. An alternative possibility is that one set of sister centromeres loses cohesin and undergoes equational segregation during anaphase I. This is the predominant pattern observed in mouse oocytes (from young females) containing a small number of univalent chromosomes (15). Segregation of a univalent pair in this manner results in a single free chromatid in the oocyte, which can then remain in the oocyte, or be ejected in the second polar body during anaphase II, resulting in either trisomy or euploidy. This outcome is consistent with the prevalence of single-chromatid aneuploidy in metaphase II-arrested human oocytes (2). It is also compatible with "correction" of meiosis I defects during anaphase II to yield a euploid maternal genome as reported from genetic studies and mathematically inferred by Tyc et al. (3). However, both sources indicate that the probability of correction during the second meiotic division declines as a function of female age, most likely as a result of defective segregation of multiple chromosomes (2, 3).

The age-related increase in the frequency of aneuploidy involving multiple chromosomes is compatible with the deterioration of chromosome architecture associated with gradual depletion of chromosomal cohesin. Studies in mouse and human oocytes indicate that the primary manifestations of this are an increase in the incidence of unpaired, or tenuously attached, homologs and an increased distance between sister centromeres (2). The latter likely impairs monopolar attachment of sister centromeres, which together with reduced centromeric cohesin and impaired recruitment of its protector (2) would favor equational segregation of sister centromeres. In support of this, high-resolution live cell imaging in mouse oocytes indicates that age-related depletion of cohesin is associated with premature resolution of chiasma and equational segregation of both sets of sister centromeres during anaphase I (16). This would result in two free chromatids with a high risk of error during anaphase II. Moreover, equational segregation of multiple chromosomes during meiosis I may destabilize the meiosis II spindle as a result of extensive failure of biorientation, further amplifying the negative impact of meiosis I errors on the fidelity of chromosome segregation during meiosis II.

The equational segregation of sister chromatids in meiosis I followed by segregation of homologous chromatids in meiosis II, reported in mouse oocytes (16), is consistent with reports of "reverse meiosis" in human oocytes (17, 18). Perhaps unsurprisingly, the model proposed by Tyc et al. (3) could not distinguish between reverse meiosis and premature loss of centromeric cohesion. However, it should be noted that their best-fit model was based on the probability of meiosis II errors when the metaphase II egg is aneuploid. Although equational segregation of sister centromeres during anaphase I contravenes all of the rules of meiosis I, the resulting metaphase II egg contains the correct number of chromosomes. It is therefore not clear whether reverse meiosis and premature separation of sister centromeres can be considered as a single entity in the best-fit model proposed by Tyc et al. (3).

In exploring the clinical utility of their modeling approach, Tyc et al. (3) performed simulations to determine the probability of obtaining at least one euploid egg, taking account of female age and the number of eggs harvested. For example, the authors determined that the probability of a 42-y-old woman obtaining a euploid embryo could be increased from 70 to 90% by doubling the number of eggs retrieved from four to eight. Taken together with ovarian function markers to predict the egg number (19),

this would enable clinicians to advise patients of the number of treatment cycles required for a reasonable chance of pregnancy.

In conclusion, the inferences derived by Tyc et al. (3) from blastocyst data largely fit with genetic analysis of human oocytes (2). Because it can infer segregation patterns from very large datasets, the modeling approach used by these authors can contribute to the development of a conceptual framework for investigating the molecular basis of human oocyte aneuploidy and its association with female age. As we gain greater mechanistic insight into the molecular regulation of female meiosis, it should be possible to further refine the models and to expand their scope for informing reproductive decisions.

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1 S. I. Nagaoka, T. J. Hassold, P. A. Hunt, Human aneuploidy: Mechanisms and new insights into an age-old problem. *Nat. Rev. Genet.* **13**, 493–504 (2012).
2 M. Herbert, D. Kalleas, D. Cooney, M. Lamb, L. Lister, Meiosis and maternal aging: Insights from aneuploid oocytes and trisomy births. *Cold Spring Harb. Perspect. Biol.* **7**, a017970 (2015).
3 K. M. Tyc, R. C. McCoy, K. Schindler, J. Xing, Mathematical modeling of human oocyte aneuploidy. *Proc. Natl. Acad. Sci. U.S.A.* **117**, 10455–10464 (2020).
4 N. Hunter, Meiotic recombination: The essence of heredity. *Cold Spring Harb. Perspect. Biol.* **7**, a016618 (2015).
5 M. Petronczki, M. F. Siomos, K. Nasmyth, Un ménage à quatre: The molecular biology of chromosome segregation in meiosis. *Cell* **112**, 423–440 (2003).
6 Y. Watanabe, Geometry and force behind kinetochore orientation: Lessons from meiosis. *Nat. Rev. Mol. Cell Biol.* **13**, 370–382 (2012).
7 D. Clift, A. L. Marston, The role of Shugoshin in meiotic chromosome segregation. *Cytogenet. Genome Res.* **133**, 234–242 (2011).
8 J. Lee *et al.*, Unified mode of centromeric protection by shugoshin in mammalian oocytes and somatic cells. *Nat. Cell Biol.* **10**, 42–52 (2008).
9 T. Hassold, P. Hunt, To err (meiotically) is human: The genesis of human aneuploidy. *Nat. Rev. Genet.* **2**, 280–291 (2001).
10 S. Wang *et al.*, Crossover interference, crossover maturation, and human aneuploidy. *BioEssays* **41**, e1800221 (2019).
11 N. E. Lamb *et al.*, Characterization of susceptible chiasma configurations that increase the risk for maternal nondisjunction of chromosome 21. *Hum. Mol. Genet.* **6**, 1391–1399 (1997).
12 D. Clift, M. Schuh, Restarting life: Fertilization and the transition from meiosis to mitosis. *Nat. Rev. Mol. Cell Biol.* **14**, 549–562 (2013).
13 R. Jessberger, Age-related aneuploidy through cohesion exhaustion. *EMBO Rep.* **13**, 539–546 (2012).
14 R. C. McCoy *et al.*, Evidence of Selection against Complex Mitotic-Origin Aneuploidy during Preimplantation Development. *PLoS Genet.* **11**, e1005601 (2015).
15 A. Kouznetsova, L. Lister, M. Nordenskjöld, M. Herbert, C. Höög, Bi-orientation of achiasmatic chromosomes in meiosis I oocytes contributes to aneuploidy in mice. *Nat. Genet.* **39**, 966–968 (2007).
16 Y. Sakakibara *et al.*, Bivalent separation into univalents precedes age-related meiosis I errors in oocytes. *Nat. Commun.* **6**, 7550 (2015).
17 J. R. Gruhn *et al.*, Chromosome errors in human eggs shape natural fertility over reproductive life span. *Science* **365**, 1466–1469 (2019).
18 C. S. Ottolini *et al.*, Genome-wide maps of recombination and chromosome segregation in human oocytes and embryos show selection for maternal recombination rates. *Nat. Genet.* **47**, 727–735 (2015).
19 A. La Marca, S. K. Sunkara, Individualization of controlled ovarian stimulation in IVF using ovarian reserve markers: From theory to practice. *Hum. Reprod. Update* **20**, 124–140 (2014).