Causes and consequences of maternal age-related aneuploidy in oocytes: a review

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ABSTRACT: Although a positive correlation between aneuploidy and maternal age was first reported almost a century ago, the underlying mechanisms remain mostly unknown. Different hypotheses regarding age-related aneuploidy rise have been presented, but so far none of them can explain its full mechanism. Age-related aneuploidy is more likely to result from complex events taking place during the entire period of germ cell development, than from the failure of one particular mechanism. Recent findings confirm that the spindle assembly checkpoint (SAC) does not control and correct kinetochore-microtubule attachments in oocytes, enabling further propagation of aneuploidy, which has occurred in the earlier phases of oogenesis. In this review we will discuss the following hypotheses: the "limited oocyte pool" hypothesis, the "two hits" hypothesis, weakened centromeric cohesion and cohesin loss, different functions of the spindle assembly checkpoint and finally, changes in global gene expression.

Keywords: aneuploidy; oocyte; maternal age; meiosis; spindle assembly checkpoint

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1. Introduction

Aneuploidy is the most frequent type of chromosomal abnormality in human oocytes and can result in early pregnancy loss, miscarriage, stillbirth, or mental retardation and developmental defects in surviving foetuses (Boue et al. 1975; Hassold and Chiu 1985; Fritz et al. 2001; Hassold and Hunt 2001). Around 5% of all clinically recognised pregnancies are monosomic or trisomic (Hassold et al. 2007). However, the vast majority of aneuploid pregnancies terminate without ever being diagnosed: monosomic embryos are not viable in all cases, and pregnancies carrying one of the three most frequent types of autosomal trisomies – 13, 18 and 21 – terminate before term in 95% of cases (Baty et al. 1994; Root and Carey 1994).

Studies lasting approximately 20 years, starting in the late 1960s on over 60 000 infants, reported 0.3% of all newborns to be trisomic (Hassold and Jacobs 1984). More recent data from the European Surveillance of Congenital Anomalies' database, from 11 European countries, reveals the same level of trisomy prevalence (as the sum of all scored cases of trisomy): 33/10 000 births (Wellesley et al. 2012). Chromosomal analysis using conventional

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cytogenetic methods allowed the estimation that over 20% of human oocytes carry numerical aberrations (Eichenlaub-Ritter 1998). Studies performed on 20 000 oocytes analyzed by FISH (analyzing chromosomes 13, 16, 18, 21 and 22) reveal an aneuploidy rate of 46.8% (Kuliev et al. 2011).

The first evidence for the positive correlation between the occurrence of Down syndrome and advanced maternal age was provided in 1933 (Penrose 1933). From that time the relationship between aneuploidy rates and increasing maternal age has been clearly proven (Hassold and Hunt 2001, 2009; Hunt and Hassold 2008, 2010; Otter et al. 2010). While only 2–3% of pregnancies in women in their twenties involve trisomic foetuses, two decades later the same finding affects 35% of clinically recognised pregnancies (Hassold and Hunt 2001, 2009; Hunt and Hassold 2008, 2010). Analysis of chromosomes 13, 15, 16, 18, 21, 22 in the first polar body (PB) of eggs earmarked for IVF, showed an increase in aneuploidy occurrence from 20% in women of 35 years old, up to 60% in 43 years of age and older (Gianaroli et al. 2010; Kuliev et al. 2011).

Humans are not the only species affected by aneuploidy in oocytes. Studies on mice, pigs and cattle revealed the occurrence of aneuploidy in their oocytes (Golbus 1981; Zackowski and Martin-Deleon 1988; Lechniak and Switonski 1998; Zuccotti et al. 1998; Duncan et al. 2009; Nicodemo et al. 2010; Hornak et al. 2011; Sebestova et al. 2012). However, while a positive correlation between maternal age and aneuploidy was observed in naturally aged mice (Duncan et al. 2009; Sebestova et al. 2012), no such correlation was observed in pigs (Hornak et al. 2011).

2. Molecular mechanisms underlying increases in aneuploidy

There is currently a clear trend for humans to have children later in life. Therefore, there is much interest in understanding the mechanisms, which may be involved in the age-related rise in aneuploidy. The following hypotheses have appeared during the past decades: (1) "limited oocyte pool" hypothesis, (2) "two-hits" hypothesis, (3) weakened centromeric cohesion and cohesin loss, (4) different function of the spindle assembly checkpoint, and (5) changes in global gene expression. In this review we will describe these hypotheses and critically evaluate them in the light of the latest research findings.

2.1. "Limited oocyte pool"

Even though it has been reported that germline stem cells are present in the ovaries of adult individuals (Johnson et al. 2004; White et al. 2012), it is generally accepted that ovarian follicles are formed during the foetal development of females. From this moment their number decreases until it reaches a critical level and menopause occurs. Around the age of 25 approximately 100 000 follicles are present in the ovaries; by the age of 45 this number has dropped to several thousands (Gougeon et al. 1994; Gougeon 1998). After reaching puberty, a subpopulation of oocytes is recruited monthly to undergo growth and become antral follicles. In humans, usually only one follicle, the most sensitive to FSH stimulation, will complete maturation and ovulate. There are, on average, 21 selectable follicles on both ovaries of women between the ages of 19–30; however, this number declines to 2–3 by the age of 40 (Gougeon 1998). The "limited oocyte pool" hypothesis suggests that the lower number of antral follicles in older women's ovaries causes the recruitment of suboptimal – premature or postmature – oocytes for ovulation (Warburton 1989). In addition, according to the oocyte selection model, cells of a higher quality are preferably selected for ovulation (Zheng and Byers 1992; Eichenlaub-Ritter 1998; Broekmans et al. 2009). If the hypothesis is correct, a higher level of aneuploidy in women with a reduced oocyte pool should be expected regardless of their age. *Vice versa*, a history of aneuploid pregnancies should predict a reduced oocyte pool size. This, however, has not been confirmed by clinical data (Warburton 2005). Because the reduction of the oocyte pool due to variable aetiology (premature ovarian failure (Nippita and Baber 2007), smoking (Yang et al. 1999; Pacchierotti et al. 2007), ovariectomy) affects women of different ages, this hypothesis clearly contradicts the correlation between the increase of aneuploidy with age.

2.2. "Two hits" hypothesis

During early embryonic development in prophase I chromosomes pair up and synaptonemal complexes form (Zickler and Kleckner 1998; Walker and Hawley 2000; Page and Hawley 2003, 2004). Later, this leads to the formation of crossing overs between non-sister chromatids of homologous chromosomes (Kleckner 2006). Resulting in the

formation of a structure called 'bivalent' by two homologous chromosomes, one from the mother and one from the father.

The "Two hits" hypothesis suggests that the number and distribution of chiasmata established in prophase I may affect chromosome segregation in meiosis I, and subsequently in meiosis II (Lamb et al. 1996; Ghosh et al. 2009, 2011. While a low number of chiasmata formed close to telomeres could lead to premature bivalent segregation, proximal or multiple chiasmata can cause the formation of disomic gamete by non-disjunction in MI (Jones 2008). According to this hypothesis, chiasmata formation is the first step in aneuploid egg genesis. During the second step, a 'susceptible' configuration of chiasmata, as described in step 1, leads to the disintegration of meiosis and, as a result, a rise in aneuploidy.

A correlation between a reduced number of recombination events and increased aneuploidy has been demonstrated in mice, yeast and *Drosophila* (Malone and Esposito 1981; Hawley 2003; Jeffreys et al. 2003).

However, studies on 400 cases of trisomy 21 of maternal meiosis I origin reveal a negative correlation between the number of 'susceptible' recombination events and maternal age: only 10% of telomeric or pericentromeric exchanges were found in a group of women over 34 years old, while in woemn younger than 29 the percentage of susceptible patterns reaches 34% (Lamb et al. 2005).

2.3. Weakened centromeric cohesion and cohesin loss

In meiosis I, homologues remain paired until anaphase I, due to chiasmata and a protein complex called 'cohesin', distal from chiasmata (Nasmyth and Haering 2005, 2009). Sister chromatids are held together by cohesin on their centromeres and pericentromeric regions (Page and Hawley 2003; Hauf and Watanabe 2004; Nasmyth and Haering 2005). The cohesion between homologous chromosomes has to be abolished (by separase cleavage) at the onset of anaphase I for proper segregation of the univalents (Buonomo et al. 2000; Kudo et al. 2006, 2009). In contrast, the centromeric cohesion between sister chromatids must stay intact until anaphase II (Petronczki et al. 2003).

This chromosome behaviour, particular for meiosis, would not be possible without the preservation of a sufficient amount of cohesin on the sister chromatid centromeres and on the chromosome arms, from the moment of the establishment of the cohesion during prenatal development until the resumption of meiosis in sexually mature females. During this period, which could last decades in humans, cohesin is maintained on chromosomes without turnover (Tachibana-Konwalski et al. 2010).

Cohesin present on sister chromatid centromeres has to be protected against separase cleavage in anaphase I, to prevent precocious segregation of sister chromatids. The shugoshins (Sgo1 and Sgo2) are the proteins which**,** among their other functions, protect cohesin against proteolysis (Kitajima et al. 2006; Xu et al. 2009), by associating with protein phosphatase 2A (PP2A) and recruiting it to sister chromatid centromeres in oocytes (Riedel et al. 2006; Rivera and Losada 2006). Separase is unable to cleave the meiotic specific subunit of cohesin REC8 dephosphorylated by PP2A, so the cohesion between sister chromatids remains intact in meiosis I. Two mechanisms, a reduced level of cohesin and insufficient centromere protection, could contribute to the rise of aneuploidy with age (Hodges et al. 2005; Vogt et al. 2008).

Experiments performed on naturally aged mice have demonstrated a decrease in chromosome associated REC8 protein, both in prophase-arrested and MI oocytes (Chiang et al. 2010; Lister et al. 2010). Cohesin loss would, however, not indicate cohesion weakness by itself. It has been shown that the intra- and inter-kinetochore distance is enhanced in old oocytes, in comparison with young oocytes. In addition, the depletion of Sgo2 in oocytes from old mice was observed (Lister et al. 2010). Disruption of the mechanisms maintaining chromosomal cohesion leads to premature segregation of univalent in oocytes from old mice (Sebestova et al. 2012). However, sister chromatids were found only after induced premature separase activation, by inhibition of its regulatory mechanisms (Chiang et al. 2011). Oocytes from old mice appeared to be more sensitive to premature separase activation than oocytes from young mice, indicating weakened cohesion.

Cohesion loss, whether due to cohesin depletion or insufficient protecting mechanisms in oocytes from older females, could lead to precocious chromosome segregation. Pre-division, however, causes approximately 60% of aneuploidies (Dailey et al. 1996; Rosenbusch 2004, 2006); the remaining 40% are caused by non-disjunction and cannot, therefore, be explained by the cohesion loss hypothesis.

2.4. Function of the spindle assembly checkpoint (SAC) in meiosis

The spindle assembly checkpoint (SAC) is the key regulatory mechanism in dividing cells, which controls anaphase entry by monitoring chromosome attachment to spindle microtubules (Musacchio and Hardwick 2002; Homer 2006; Musacchio and Salmon 2007; Musacchio 2011; Akiyoshi and Biggins 2012; DeLuca and Musacchio 2012). In mitosis, one unattached kinetochore is sufficient for producing the 'wait anaphase signal' and arresting the cell cycle in metaphase (Nicklas and Arana 1992; Malmanche et al. 2006). Subsequently, a mechanism involving Aurora B kinase, and other components, corrects the improperly attached chromosomes (Lampson et al. 2004; Shuda et al. 2009; Lampson and Cheeseman 2011).

The presence of the SAC in oocytes has been proven by their arrest in metaphase I upon exposure to the microtubule-depolymerising drug nocodazole, resulting from kinetochore-microtubule attachment disruption (Duncan et al. 2009; Lister et al. 2010; Sebestova et al. 2012). It has also been demonstrated that depletion of core SAC components, such as Mad2, Bub1 and BubR1, causes premature chromosome segregation and anaphase I onset (Homer et al. 2005; McGuinness et al. 2009; Wei et al. 2010).

However, the presence of the SAC in both mitosis and meiosis does not necessarily indicate a similar function. Research has shown that a critical mass of approximately 80% of the chromosomes correctly aligned on the metaphase plate is sufficient to satisfy the SAC and allow a cell to proceed to anaphase in meiosis I (Nagaoka et al. 2011). Measuring the intensity of the 'wait anaphase signal' of chromosomes on the equatorial plane and spindle poles demonstrates that this signalling and its dynamics are not dependent on chromosome position (Gui and Homer 2012). Additional research has confirmed these findings, demonstrating that SAC silencing at the onset of anaphase-promoting complex/cyclosome (APC/C) activity in meiosis I takes place despite the fact that chromosomal congression on the metaphase plate is not yet achieved (Lane et al. 2012).

The latest publication on this topic by Sebestova et al. shows that multiple unaligned chromosomes are not competent either to arrest or delay metaphase-to-anaphase transition in meiosis I (Sebestova et al. 2012). This clearly indicates that in meiosis the SAC functions only as a 'timer' for APC/C activation.

2.5. Global gene expression and DNA methylation

An alternative hypothesis pointing to the influence of maternal age on global gene expression has been offered as an explanation for the increase in aneuploidy with age (Jones 2008).

Global gene expression changes during oocyte development (Schultz 2005). While the transcript in oocytes from old and young mice are similar, the transcriptome in eggs differs significantly (Hamatani et al. 2004; Pan et al. 2008). However, further research into the effect of decreased transcription on gene function, for example of DNA methyltransferases, showed no differences in the methylation of differentially methylated regions in imprinted genes (Lopes et al. 2009), calling in to question the significance of decreased global gene expression for the developing embryo.

3. Conclusion

Aneuploidy is the leading cause of reduced fertility in females and developmental abnormalities in foetuses. None of the different hypotheses which have been advanced to explain the age-related increase in rates of aneuploidy could so far explain the mechanism completely. The incidence of aneuploidy in oocytes from older females appears to be rather the result of several events than an insufficiency in one mechanism. The number and distribution of chiasmata formed during early prophase I as well as weakened centromeric cohesion, establish a strong predisposition for aneuploidy. This, in combination with the absence of a mechanism, which detects and corrects erroneously attached chromosomes in oocytes, results in an increased possibility of aneuploid egg formation and – more importantly – the propagation of aneuploidy in the newly developing embryo.

New findings about SAC function in oocytes have imparted an impulse toward the re-valuation of the roles played by different mechanisms in age-related aneuploidy, demonstrating that further investigation is required.

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