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Maternal age and chromosomally abnormal pregnancies: what we know and what we wish we knew

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Abstract

Purpose of review—The relationship between increasing maternal age and trisomy has been recognized for over 50 years and is one of the most important etiological factors associated with any human genetic disorder. Specifically, the risk of trisomy in a clinically recognized pregnancy rises from about 2–3% for women in their twenties to an astounding 30% or more for women in their forties. Thus, as women approach the end of their child-bearing years, errors of chromosome segregation represent the most important impediment to a successful pregnancy.

Recent findings—Despite the clinical importance of this relationship, we do not understand how age affects the likelihood of producing a normal egg. Errors that affect chromosome segregation could occur at several stages during the development of the oocyte: in the fetal ovary, either during the mitotic proliferation of oogonia or the early stages of meiosis; in the “dictyate” oocyte, during the 10–50 year period of meiotic arrest; or during the final stages of oocyte growth and maturation, when meiosis resumes and the meiotic divisions take place. Recent evidence from studies of human oocytes and trisomic conceptions and from studies in model organisms implicates errors at each of these stages

Summary—It seems likely that there are multiple causes of human age-related nondisjunction, complicating our efforts to understand – and, ultimately, to provide preventative measures for – errors associated with increasing maternal age.

Keywords

trisomy; maternal age; recombination

Introduction

The association between advancing maternal age and trisomy is one of the best-known and longest recognized risk factors for any human genetic defect. As early as 1933 – a quarter century before the identification of trisomy 21 by Lejeune et al [1] – Penrose recognized that Down syndrome was more common in older women [2]. Studies in the 1960–1980s confirmed and extended these observations, and it is now clear that increasing age of the women increases the likelihood of trisomy for most, if not all, human chromosomes [3,4]. However, our understanding of the basis of the age effect has not matched our understanding of the clinical

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importance of the effect; indeed, we know little more about the underlying causes of the age effect than did either Penrose or Lejeune.

Fortunately, this situation may finally be changing. Large-scale analyses of the origin of trisomy 21, new approaches to the study of human gametes, and mutational analyses of model organisms have begun to shed light on processes that mediate nondisjunctional risks. In this review, we summarize these observations in four steps: first, reviewing the stages of oocyte development; second, summarizing recent analyses of human trisomies; third, reviewing recent studies of meiosis in human oocytes; and finally, discussing recent advances in our understanding of nondisjunction from meiotic analyses of model organisms.

The life cycle of the human oocyte: a complicated journey

It is perhaps not surprising that most human trisomies are maternally-derived, since the life cycle of the oocyte is long and complicated. In both the fetal ovary and testis the germ cells undergo a period of mitotic proliferation, but the two pathways soon diverge. Shortly after the onset of testis differentiation, male germ cells cease proliferating and enter into a protracted arrest phase. In contrast, in the ovary female germ cells enter meiotic prophase during the first trimester of pregnancy in response to meiosis-specific inducers such as *Stra8* (e.g., [5]) (Figure 1). Over the next several weeks a complicated series of chromosomal events occur, with homologous chromosomes first finding and synapsing with one another and ultimately exchanging genetic material, or recombining. Shortly thereafter, the process grinds to a halt, and oocytes enter an arrest phase, termed dictyate. The prophase-arrested oocyte remains in a state of meiotic suspended animation until it is eliminated by atresia or, following the onset of menses, is recruited into the pool of growing oocytes. On average, one oocyte per ovarian cycle completes the first meiotic division (MI) and proceeds to metaphase of meiosis II (MII); if fertilized by a sperm, it completes the second division and embryonic development ensues. Thus, over the approximate 30 year reproductive lifetime of a human female, only a few hundred oocytes complete the first meiotic division and few – if any – complete the second.

Because the oocyte remains in prophase arrest for most of its lifetime, abnormalities arising during this stage seem the most obvious candidates for the genesis of the age effect. However, as detailed below, there is growing evidence that the pre-meiotic mitotic divisions, meiotic prophase, and the meiotic divisions all contribute as well.

Studies of the origin of human trisomies: the when and who of meiotic nondisjunction

In the late 1980s, a number of investigators took advantage of DNA polymorphism analysis to analyze the origin of the extra chromosome in human trisomies. Two decades later, over 1,500 cases have been examined; the majority derive from maternal meiotic errors, and absent or altered meiotic recombination is an important contributing factor in all trisomies studied (for review, see [6]). There are, however, important chromosome-specific differences, as evidenced by recent data on two “under-studied” trisomies (13 and 22). In studies of trisomy 22 Hall et al [7] reported a preponderance of maternally-derived cases, typically arising from MI nondisjunction and frequently involving failure of recombination between the homologs. The results were similar for trisomy 13, although with a higher proportion of cases of maternal MII origin [8,9]. Hall et al [7] compared their observations on trisomy 22 with trisomies involving other acrocentric chromosomes and with non-acrocentric trisomies and concluded that there are at least three different nondisjunctional patterns: those that apply to all chromosomes, those that apply to groups of chromosomes (e.g., trisomies involving acrocentric chromosomes, since maternal MI errors and recombination failure are features of these), and those that are chromosome-specific (e.g., trisomy 16, since it is almost always due to maternal

MI errors but – unlike other trisomies – has no apparent contribution of recombination failure). This suggests the existence of multiple nondisjunctional mechanisms and, presumably, more than one age-related route to mal-segregation.

The relatively small number of available cases has precluded detailed comparisons of nondisjunctional mechanisms involving younger and older women. Trisomy 21 -- and in particular, one study of trisomy 21 -- provides a notable exception. Beginning in 1992, Sherman and colleagues initiated a long-term molecular and epidemiological study of trisomy 21. Initially restricted to the metropolitan Atlanta, Georgia area, the study was expanded to include five other U.S. sites [10], and now includes data on parent and meiotic stage of origin for 1,070 non-mosaic cases of trisomy 21 [11]. Several important observations have emerged from this study: (1) the vast majority of cases of trisomy 21 (approximately 95%) are maternal in origin, typically deriving from errors at MI, (2) maternal MI errors are associated with failure to recombine or with distally located exchanges, (3) cases scored as arising at maternal MII are also associated with altered recombination – in this instance extremely proximal exchanges – suggesting that they actually derive from recombination errors that affect MI segregation, and (4) paternally-derived cases of trisomy are more likely to involve MII than MI errors, and are not associated with alterations in recombination [11–13].

This study has also provided intriguing – if puzzling -- information regarding the maternal age effect. First, both maternal MI and so-called MII errors increase with maternal age, providing evidence for different age-related nondisjunctional mechanisms. Second, the association between altered recombination and maternal age is complex, and varies among the different categories of recombination defects. That is, the importance of distally located exchanges in maternal MI errors declined with increasing maternal age, while the opposite effect was observed for pericentromeric exchanges in MII errors. Further, the proportion of MI cases associated with recombination failure was highest among the youngest women (under 30 years of age), decreased in women between 30–34 years, and increased in the oldest age category. While the meaning of these different age-related changes in recombination status is not yet clear, it seems likely that, for at least some errors, the oocyte is “set up” to nondisjoin because of sub-optimal recombination events. Thus, the link between events occurring in the fetal oocyte (meiotic recombination) and nondisjunctional errors occurring decades later seems clear, and the evidence from studies of trisomies suggests that multiple mechanisms are involved in the genesis of human trisomies.

What the human fetal oocyte has to tell us

The above studies provide indirect evidence that events occurring in the fetal oocyte influence the likelihood of nondisjunction at MI or MII. However, the difficulties associated with acquisition and analysis of fetal ovarian material have prevented us from directly testing this assertion; e.g., by asking whether the unusual cross-over configurations suggested by studies of trisomies can actually be visualized in meiotic chromosome preparations. Fortunately, the technology to conduct these analyses has finally become available (e.g., [14]), and several groups have now used this approach to examine the early stages of meiosis in the human female (e.g., [15–18]). While the experimental details vary among the studies, the basic approach is the same: immunostaining is used to visualize the synaptonemal complex (SC; the meiosis-specific structure that mediates synapsis between homologs), as well as SC-associated recombination machinery proteins responsible for the formation or processing of programmed double strand breaks into meiotic recombination events (cross-overs). The mismatch repair protein MLH1 has been especially useful in these studies: it loads onto the SC at sites where cross-overs will form, and thus serves as a convenient marker for recombination events (Figure 2).

Several general principles have emerged from these cytological studies: (1) The number of MLH1 foci (cross-overs) per human oocyte is variable among individuals; however, taken together, oocytes have more MLH1 foci than do human spermatocytes, and the location of the foci displays sex-specific differences – in males distal foci predominate, while in females they are more likely to be interstitial on the chromosome arms [19,20]. These observations are consistent with genetic linkage results [21–24], and indicate that meiotic recombination is controlled differently in females than in males. (2) The basic “rules” of meiosis apply to human females as they do to human males and other mammals; e.g., in general each chromosome arm contains at least one MLH1 focus, and when multiple foci are observed on the same chromosome they are “spread out”, consistent with the meiotic property of chiasma interference [20,25]. (3) However, against this background, the early events of human female meiosis appear to be less tightly regulated than in human males or mouse males or females. For example, in mice and in human males MLH1 localization occurs over a narrow temporal window, while in females it occurs during a much wider timeframe [17,20,25]. Further, the level of synaptic defects is astonishingly high in human oocytes; indeed, Hulten and colleagues have suggested that a majority of early prophase human oocytes display fragmentation and/or defective synapsis [15]. Finally, although most chromosomes exhibit at least one MLH1 focus, a surprisingly high proportion do not; in fact, a recent study of human pachytene oocytes suggests that as many as 5% of chromosomes 21 may be “cross-over less” [20]. Thus, from these analyses one is left with the impression that the early events of meiosis are somewhat “sloppier” in the human female than in the human male or other mammals.

While these studies have provided basic information on the early events of oogenesis, do they have any relevance to nondisjunction? Several investigators suggest that the answer is yes. Of particular importance, Cheng and colleagues recently provided evidence that the unusual cross-over configurations predicted from studies of trisomies are, indeed, present in fetal oocytes [20]. For example, trisomy 16 is thought to be associated with distal exchanges but not with failure to recombine, while trisomies 18, 21 and 22 have been attributed to recombination failure. Consistent with this, in fetal oocytes Cheng et al [20] observed distally located MLH1 foci – but not “MLH1-less” bivalents -- for chromosome 16, while the latter situation was common for chromosomes 18, 21 and 22. From this they suggested that different chromosomes have different routes to age-independent and age-dependent nondisjunction, but that at least some of the cases are “set-up” to nondisjoin because of prenatal events. Similarly, Lenzi et al [17] observed a ten-fold difference in the number of MLH1 foci in individual oocytes, and suggested that as many as 30% of human oocytes might be predisposed to nondisjunction because of events occurring in fetal oogenesis. Finally, Hulten and colleagues [15] observed lower MLH1 values in fetal oocytes with synaptic defects and suggested that, if these oocytes were able to survive and contribute to the adult oocyte pool, they would be susceptible to nondisjunction.

Not all investigators are of the same opinion. In a recent study of prophase oocytes, Robles et al [16] examined the distribution of different recombination proteins on chromosome 21 and concluded that prenatal events are unimportant in the genesis of trisomy 21. However, on the surface this is a somewhat puzzling conclusion, since approximately 4% of chromosomes 21 were “MLH1-less” and were thus presumably nondisjunction-prone. More intriguingly, Hulten et al [26] recently provided a completely different take on the maternal age effect. Using chromosome 21 fluorescence in situ hybridization (FISH) probes to analyze fetal ovarian cells from eight female fetuses, they reported a surprisingly high level of trisomy 21 mosaicism. They postulated that such trisomy 21 oocytes might be delayed in their development and, as a result, would be ovulated later in life than chromosomally normal oocytes. If true, the effect of age – at least for chromosome 21 – would be due to the fact that the pool of growing follicles containing a trisomic oocyte increases with age, not because the incidence of nondisjunction of chromosome 21 increases in normal oocytes. Clearly these observations need to be

confirmed – and extended to other chromosomes -- but the implication of this hypothesis is that the age effect may be “pre-destined” to occur because of events occurring even before oocytes enter meiosis.

Lessons from model organisms

The difficulties associated with analysis of human female meiosis – the long life cycle of the oocyte, ethical and technical considerations surrounding collection of study material, and the absence of an *in vitro* model system -- make animal models an attractive alternative. Over the past few years, this approach has yielded interesting dividends with regard to our understanding of meiotic recombination, as well as insights into possible molecular mechanisms of meiotic nondisjunction.

How are recombination levels controlled?

Because alterations in recombination play a central role in meiotic nondisjunction, an obvious question arises: what determines the number and location of recombination events in the first place? In two recent studies of mice, different groups reported a “trans-regulator” of recombination in the same chromosome region. That is, both Grey et al [27] and Parvanov et al [28] observed changes in recombination levels in non-chromosome 17 regions in association with allelic variation in a region of chromosome 17. However, not all changes in recombination levels were linked to chromosome 17 genotypes, indicating the existence of other, as yet unknown, recombination-associated loci. The importance of this observation to nondisjunction is straightforward. Allelic variation at recombination-setting loci may lead to individuals whose gametes are more likely to contain chromosomes with “unfortunate” cross-over configurations (e.g., absence of an exchange between homologs), resulting in a genetic predisposition to aneuploidy. With the uncovering of additional recombination-setting loci in mice and humans (e.g., [29]) it should be possible to ask whether such an association does, indeed, exist.

What is the molecular basis of maternal-age related nondisjunction?

While studies of human trisomies and of fetal oocytes have provided a wealth of information on the nature of human nondisjunction and the maternal age effect, the underlying molecular lesions remain unknown. Recent studies of model organisms have now provided an intriguing list of suspects, including some that act before the time of chromosome segregation and some that act at or around the time of segregation (for a detailed review of some of these, see [30]. Among the “earlier”-acting agents, sister chromatid cohesion proteins provide attractive candidates. These join to form the multi-protein cohesin complex that holds sister chromatids together prior to cell division; cohesin is especially important in meiosis I, where it helps maintain connections between the homologous chromosomes. Recent evidence from two model organisms suggests a role of cohesins in generating the maternal age effect. First, in an elegant series of experiments, Bickel and colleagues generated a system to monitor the effect of aging on *Drosophila* oocytes [31], and identified age-related increases in aneuploidy in situations in which cohesin was perturbed [32,33]. Importantly, they were able to demonstrate effects on both “exchangeless” and “exchange” homologs, suggesting that age-related deterioration of cohesin affects segregation of chromosomes with either cross-over configuration. Studies of female mice have yielded similar results. Specifically, Hodges et al [34] monitored chromosome behavior at meiosis I in oocytes from females homozygous for a null mutation in the meiotic cohesin *Smc1/2* and identified remarkable increases in unpaired homologs and sister chromatids in 4 month-old mice over those observed in 2 month-old mice. Thus, results from two species suggest that deficient cohesin may be an underlying cause of age-related nondisjunction in humans.

Among candidates acting nearer the time of chromosome segregation, defects in cell cycle control – specifically, in the spindle assembly checkpoint (SAC) – have received considerable attention (for review, see [35]). Several lines of evidence support an association between age-related declines in the strength of the SAC and increasing aneuploidy levels. For example, in oocytes of both mice and humans, expression studies indicate age-related reductions in transcripts of several checkpoint-associated loci [36,37]. Further, in studies of mice deficient for the checkpoint protein BubR1, Baker et al [38] observed progeroid phenotypes, as well as infertility and increased levels of meiotic aneuploidy in females. Similarly, Niault et al [39] identified increases in meiosis I errors in female mice heterozygous for the checkpoint protein Mad2. Thus, the results of a recent study directly testing the importance of the SAC in mediating age-related aneuploidy were somewhat surprising. That is, Duncan et al [40] were unable to demonstrate differences in timing of the onset of anaphase I between oocytes of young and old female mice. Consequently, while SAC-associated defects remain an appealing candidate for maternal-age related aneuploidy, confirmation of this relationship is still lacking.

Although many of the recent studies of age-related aneuploidy have focused on sister chromatid cohesion or the SAC, a number of other possible culprits remain. For example, defects in the formation of the synaptonemal complex [41], in the maintenance of telomeres [42], and in levels of histone acetylation [43] have all been linked with meiotic defects in female mice and thereby implicated in the etiology of age-related aneuploidy in humans. Thus, the weight of evidence from these and other studies summarized in this review indicates that there are multiple causes of age-related meiotic errors. Consequently, rather than searching for “the cause” of the maternal age effect, we need to adjust our thinking and view the maternal age effect as a spectrum of defects with multiple underlying mechanisms.

Summary

The data summarized in this review allow us to draw two important conclusions. First, while we have long known that human female meiosis is error-prone, the occurrence of synaptic and recombination defects in fetal oocytes and the correlation between altered recombination and human trisomies make it clear that the problem is not just restricted to the meiotic divisions. Indeed, it seems likely that some proportion of oocytes are “set up” to nondisjoin because of events occurring in the fetal ovary. Second, contrary to common opinion the most important risk factor for aneuploidy – increasing maternal age – is not a single entity. Age affects individual chromosomes differently and for some chromosomes there are likely many routes to age-related nondisjunction. Thus, although finding the cause of the human maternal age effect remains the holy grail of aneuploidy research, we need to recognize that there is not just one age-related mechanism. In future investigations our challenge will be to determine which of the above – or other – molecular lesions is relevant to which chromosome, and which is most important to clinical disorders such as Down syndrome.

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Figure 1.

Life cycle of the human oocyte. There are several different timepoints at which events may occur that increase the likelihood of meiotic nondisjunction in older women; examples of some of these events (and the references supporting their importance) are provided.

Figure 2. Representative image of a human fetal prophase oocyte. Antibodies detect the synaptonemal complex protein SYCP3 (in red) and the DNA mismatch repair protein MLH1 (in green) and CREST antiserum-positive signals (in blue) detect centromeric regions.