Chromosomal non-disjunction in human oocytes: is there a mitochondrial connection?

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The frequency of chromosome abnormalities due to non-disjunction of maternal chromosomes during meiosis is a function of age, with a sharp increase in the slope of the trisomy-age curve between the ages of 30 and 40 years. The basis of this increase, which is a major cause of birth defects, is unknown at present. In recent years, mutations in mitochondrial (mt) DNA have been associated with a growing number of disorders, including those associated with spontaneous deletions of mtDNA (ΔmtDNAs). Intriguingly, these pathogenic ΔmtDNAs, which are present at extremely high levels in certain patients, are also present at extremely low levels (detectable only by polymerase chain reaction) in normal individuals. The proportion of such ΔmtDNAs in normal muscle is a function of age; the shape of this curve is exponential, with the accelerating part of the curve beginning at ~30–40 years. We postulate that, as well as muscle and brain, a similar time-dependent accumulation of ΔmtDNAs also occurs in normal oocytes. Since ΔmtDNAs are functionally inactive, an accumulation of such aberrant genomes could eventually compromise ATP-dependent energy-utilization in these cells. Furthermore, these deficiencies would also affect the function of the somatic follicular cells that surround, and secrete important paracrine factors to, the oocyte. If there is indeed an age-associated relationship between ΔmtDNAs and oocyte age, perhaps errors in meiosis (which is almost certainly an energy, and ATP, dependent process) are related to mutations in mtDNA (primarily deletions, but perhaps point mutations as well) in oocytes and/or the surrounding somatic cells, which result in deficiencies in both mitochondrial function in general and oxidative energy metabolism in particular. This hypothesis would explain many of the non-Mendelian features associated with maternal age-related trisomies, e.g. Down’s syndrome.
**Key words:** ageing/Down’s syndrome/meiosis/mitochondrial disease/mitochondrial DNA

**Introduction**

The study of mammalian female meiosis provides us with a fascinating challenge: meiosis is not only protracted over several years, but the overall process arrests twice, both in meiosis I (MI) and meiosis II (MII). The primordial germ cells are first seen in fetal life among the endodermal cells of the yolk sac at 4 weeks, and following migration to the gonadal ridge, undergo rapid mitoses, leading to \(\sim 7 \times 10^6\) oogonia by 20 weeks. These cells lose their ability to undergo further mitotic division and subsequently enter meiosis. The exact mechanism that initiates meiosis is not precisely defined. Ovarian stromal (pregranulosa) cells surround these primary oocytes, thus forming the primordial follicles that will remain in the dictyate stage of meiosis until maturation of the hypothalamic–pituitary axis at puberty. The majority of these follicles will undergo various stages of maturation and atresia, so that at birth only \(2 \times 10^6\) germ cells will remain (Peters et al., 1976). This process of atresia is an ongoing one, proceeding throughout infancy and childhood.

With the maturation of the human female reproductive system, a dominant follicle will emerge from within a cohort of early stage follicles. As a result of precise hormonal control, including autocrine and paracrine signalling, this maturing follicle will continue through the full spectrum of follicular development. These stages include the primary, preantral, and antral follicular stages, whereupon the oocyte is surrounded by the somatic cumulus granulosa cells and the Call–Exner bodies coalesce into a single antrum containing the follicular fluid. Following the surge of luteinizing hormone that presages ovulation, meiosis resumes, as evidenced by germinal vesicle breakdown and extrusion of the first polar body. Meiosis will then proceed until metaphase in MII and will remain arrested until fertilization.

**Inhibition and resumption of meiosis**

For the purposes of understanding meiotic control of oocytes, it is helpful to divide follicular development into two stages, preantral and antral. When removed from a late stage antral follicle, the oocyte has the capacity to resume and continue meiosis unhindered to MII (Edwards, 1965), a property that preantral oocytes do not have. Furthermore, co-culture of the stripped oocytes with granulosa cells and follicular fluid inhibits meiosis (Tsafriri and Pomerantz, 1984; Sirard and Bilodeu, 1990). These important observations would indicate that the inhibition of meiosis in the preantral oocyte is a result of incomplete development within the cell itself. Conversely, the mature antral oocyte is responding to inhibitory signals from the surrounding somatic cells and to factors within the follicular fluid. These experiments also demonstrate that the oocyte must undergo inherent changes to become competent to resume meiosis. In murine models, nuclear competence appears to require both the presence of follicular somatic cells (Byskov et al., 1997) as well as the acquisition of the constituents that are necessary for cell cycle transition. Maturation promoting factor (MPF) is required for the resumption of meiosis; it increases in the oocyte even in the absence of somatic cells (Eppig et al., 1993). However, nuclear maturation factors do not act in isolation; rather it is the interplay of extrinsic cell signalling with intrinsic cell cycle regulators such as MPF that is critical for the acquisition of nuclear competence in the oocyte (Chesnel et al., 1994).
Age-related changes in maturing oocytes and follicles

One of the recognized changes in the nuclear envelope of the mature oocyte is the appearance of microtubule organizing centres (MTOCs) that will later be used in assembly of the meiotic spindle. Microtubule motor proteins are associated with the microtubules and the chromosomes, particularly the kinetochore (de Pennart et al., 1994) and centrosomes (Battaglia et al., 1996a), and actively participate in the arrangement and preservation of the spindle structure. In ageing human oocytes, irregularities in spindle formation and chromosome alignment have been identified (Battaglia et al., 1996b). The actual aetiology for these changes remains unclear, with a number of different hypotheses proposed. The possibility of inherent time-dependency in the breakdown of the spindle components themselves has been suggested (Hawley et al., 1994). However, the astute suggestion has been made that it could be the necessary stockpiling of proteins necessary for nuclear development that is impaired and that ultimately leads to non-disjunction in ageing oocytes (Hunt and LeMaire-Adkins, 1998). Of note, changes not just within the oocyte but in overall follicular functional maturation, such as decreased time to ovulation, have been observed in humans (Klein et al., 1996).

Mitochondrial DNA and mitochondrial disease

The human mitochondrial genome (Figure 1) is a 16 569 bp circle of double-stranded DNA (Anderson et al., 1981). It contains genes encoding two ribosomal RNAs and 22 transfer RNAs, as well as 13 structural genes that encode subunits of components of the respiratory chain complexes. Of the 13 structural genes, seven encode subunits of complex I (NADH-coenzyme Q oxidoreductase), one encodes the cytochrome b subunit of complex III (CoQ-cytochrome c oxidoreductase), three encode subunits of complex IV (cytochrome c oxidase, or COX), and two encode subunits of complex V (ATP synthetase). Each of these complexes also contains subunits encoded by nuclear genes, which are imported from the cytoplasm and assembled, together with the mtDNA-encoded subunits, into the respective holoenzymes, each of which is located in the mitochondrial inner membrane. Complex II (succinate dehydrogenase-CoQ oxidoreductase), of which succinate dehydrogenase (SDH) is a component, is encoded entirely by nuclear genes; SDH thus serves as an independent marker for mitochondrial number and activity.
Mitochondria (and mtDNAs) are maternally inherited (Hutchison et al., 1974; Giles et al., 1980). Thus, pathogenic mutations in mtDNA normally (but, importantly, not always) result in pedigrees that exhibit maternal inheritance, i.e. the disease passes only through females, and essentially all children (both boys and girls) inherit the error. In addition, because there are hundreds or even thousands of mitochondria in each cell, with an average of five mtDNAs per organelle in somatic cells (Satoh and Kuroiwa, 1991), mutations in mtDNA typically result in two populations of mtDNAs (i.e. wild-type and mutated), a condition known as heteroplasmy.

An ever-growing number of diseases are due to maternally inherited mtDNA point mutations (reviewed in Schon et al., 1997). Point mutations in mtDNA-encoded respiratory chain polypeptides are responsible, in the main, for Leber’s hereditary optic neuropathy (LHON); neuropathy, ataxia, and retinitis pigmentosa (NARP); and maternally inherited Leigh syndrome (MILS). The great majority of mtDNA point mutations, however, are in the tRNA genes. The most prominent of these disorders are mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS); myoclonus epilepsy with ragged-red fibres (MERRF); and a mixed group of maternally inherited myopathies, encephalomyopathies, and cardiomyopathies (Schon et al., 1997).

Large-scale rearrangements of mtDNA, i.e. partial deletions (ΔmtDNAs) and partial duplications (dup-mtDNAs), are also associated with disease. The most common pathologies are ocular myopathy (OM) and the Kearns–Sayre syndrome (KSS), two mitochondrial disorders associated with progressive external ophthalmoplegia (PEO) (Holt et al., 1988; Zeviani et al., 1988; Moraes et al., 1989), as well as a haematopoietic disorder called Pearson’s marrow/pancreas syndrome (PS) (Rötig et al., 1989). In these disorders, the ΔmtDNAs can be observed easily by Southern blot hybridization analysis as a large population (up to 80% of total mtDNA) of mtDNA molecules migrating in electrophoretic gels more rapidly than full-length mtDNAs. Importantly, these three syndromes are almost never maternally inherited, as the deletions arise spontaneously in the patient whose mother and siblings are usually normal, both phenotypically and genetically. In addition, the deletions are unique in each patient, with the particular type of deletion differing among patients; however, about one-third of all KSS/PEO/PS patients harbour the same deletion, called the ‘common deletion’ (Schon et al., 1989; Mita et al., 1990), which removes 4977 bp of mtDNA between the ATPase8 and ND5 genes (see Figure 1). Taken together, these findings imply that the ΔmtDNA population in any one such patient is a clonal expansion of a single spontaneous deletion event occurring early in oogenesis or in embryogenesis.

Some mtDNA rearrangements are maternally inherited, but these patients do not have the clinical features of KSS or PEO; they more typically have maternally inherited type II diabetes (Dunbar et al., 1993). Significantly, mtDNA duplications, but not mtDNA deletions, have been documented to be inherited in this way. With but one exception (S.DiMauro, personal communication), there is no convincing evidence that large-scale mtDNA deletions can be inherited through the female germline, implying that high levels of ΔmtDNAs (but, somewhat surprisingly, not equivalently high levels of pathogenic mtDNA point mutations) are incapable of being transmitted to viable offspring.

Besides the ‘clonal’ mtDNA deletions found in the sporadic rearrangement disorders, a number of Mendelian-inherited disorders in which affected family members harbour large quantities of multiple species of deletions of mtDNA in tissues (usually muscle) have been described. These deletions are apparently gen-
erated during the lifespan of the patient (Zeviani et al., 1989; Nishino et al., 1999).

Intriguingly, while most mtDNA point mutations can be maternally transmitted (and maternally inherited), a growing group of mutations appear to violate this dictum. Of the few known sporadic mtDNA point mutations or microdeletions (~10% of all point mutations), almost all are located in polypeptide-coding genes. While they are predominantly in the cytochrome b subunit of complex III (Dumoulin et al., 1996; Andreu et al., 1998, 1999a), these mutations have also been found in other complexes (Keightley et al., 1996; Hanna et al., 1998; Andreu et al., 1999b). The prevalence of sporadic mutations in mtDNA-encoded polypeptides implies that, like ΔmtDNAs, the loss of a functional respiratory chain somehow selects against viable progeny in the germline.

Deletions of mtDNA in somatic tissues during normal ageing

In the last few years it has become clear that tissues from normal individuals, especially terminally differentiated (post-mitotic) tissues with high oxidative requirements, e.g. muscle and brain, contain low amounts of ΔmtDNAs (Schon et al., 1996). These deleted mtDNAs, which are observable only after amplification using the polymerase chain reaction (PCR), are qualitatively identical to the highly abundant populations of ΔmtDNAs that have been described in patients with sporadic PEO and KSS, sporadic Pearson’s syndrome, and autosomal-dominant PEO.

Importantly, the ΔmtDNAs found in normal individuals appear to accumulate during ageing. Using a quantitative PCR technique to measure the amount of the common deletion, we have found that this species of ΔmtDNA accumulates in muscle by a factor of 10,000 over the course of the normal human lifespan, reaching a level of ~0.1% of total muscle mtDNA by the age of 84 years (Simonetti et al., 1992; Pallotti et al., 1996). Besides the common deletion, numerous other deleted species are also present in ageing muscle (Zhang et al., 1992; Chen et al., 1993; Pallotti et al., 1996). Thus, both the overall number of different ΔmtDNA species, and the amount of each such species, increases with time, such that, in the aggregate, perhaps as much as 5–10% (or, according to some workers, even more) of total mtDNA is deleted in elderly individuals. These ΔmtDNAs are not distributed homogeneously, at least in muscle. Rather, individual muscle fibres appear to contain the majority of deleted molecules (Schon et al., 1996; Brierley et al., 1998), and it is these fibres that are respiratorily deficient.

Presence of mtDNA deletions in normal human oocytes

We currently do not know why, or how, ΔmtDNAs accumulate with age. A logarithmic increase in ΔmtDNAs with respect to age would be consistent with the idea that ΔmtDNAs are competent for replication, and the ΔmtDNAs observed at later ages are progeny of ΔmtDNAs that arose earlier in time. This exponential accumulation of ΔmtDNAs poses an interesting mechanistic question. ΔmtDNAs appear to arise afresh with each generation, as our data indicate that there are four orders of magnitude fewer ΔmtDNAs in infancy as compared to old age. If this is true, how can a woman of childbearing age, who already harbours a low but detectable level of ΔmtDNAs (at least in her somatic tissues), give birth to a baby containing almost no ΔmtDNAs at all? In other words, how does the organism ‘reset’ the level of mtDNA mutations in each generation? This may be due to one of at least three possibilities: (i) ΔmtDNAs arise and accumulate in somatic tissue, but do not arise in female germline tissue (a hypothesis proposed by Nagley et al.,
Maternal meiotic non-disjunction resulting in aneuploidy shows a very strong relationship with increasing maternal age, with an exponentially rising curve after ~32 years. This maternal age effect holds for all chromosomal pairs, with the exception of the very large chromosomes (where there seems to be little maternal age effect) and for chromosomes 2 and 16 (where the effect is linear) (Warburton and Kinney, 1996). It has been estimated that at least 30% of oocytes in women aged >40 years have undergone non-disjunction.

These findings have stimulated us and others (Jansen and De Boer, 1998; Van Blerkom et al., 1998) to consider the possibility that an age-related increase in mtDNA mutations in oocytes could be an underlying cause of the maternal age effect on chromosomal non-disjunctions. Specifically, we postulate that, as a woman ages, mtDNA mutations accumulate in her oocytes, and that the frequency of aneuploidy increases once a threshold of mitochondrial energy deficit is crossed. As described above, the process of meiotic inhibition and resumption is the result of the production of autonomous factors by the oocyte, as well as the response to extrinsic signalling by the surrounding follicular cells. Consequently, mtDNA mutations that accumulate over time in the surrounding somatic cells might also lead to aneuploidy. This ‘mitochondrial ageing hypothesis’ would explain the relationship between maternal age and the frequency of trisomies, e.g. Down’s syndrome.

The idea that oocytes require high concentrations of ATP (Van Blerkom and Runner, 1984; Van Blerkom, 1991) and that a mitochondrial energy deficit could result in aneuploidies is not a new one (Beermann and Hansmann, 1986). However, the most compelling reason to consider a mitochondrial aetiology in germline aneuploidies may be that there are no mechanistic data that explain successfully the age-related increase in human trisomies. Specifically, no data exist to explain why the mere passage of time should result in the increased frequency of non-disjunction events. An age-related phenomenon can be the result, of course, of age-related changes in nuclear DNA, or to epigenetic and environ-
mental factors, but it is more difficult to invoke these causes (which probably vary from individual to individual) to explain the consistent and specific observation of age-related aneuploidies, which show little or no variation with geographical region, ethnicity, or social class. On the other hand, the ‘mitochondrial paradigm’, with its focus on population genetics, on random but cumulative effects of mutations, on heteroplasmy (and, in ageing, ‘polyplasmy’), and on mitotic segregation (coupled with the mitochondrion’s monopoly in oxidative energy metabolism) is an attractive alternative hypothesis to explain the ageing–aneuploidy correlation.

Other facts also support a mitochondrial aetiology. As noted above, there is an exponential increase in the amount of the common deletion in muscle over time (Simonetti et al., 1992; Pallotti et al., 1996). The shape of this curve roughly parallels the curve describing the increase in the frequency of trisomies as a function of maternal age (Penrose, 1933; Hassold and Jacobs, 1984; Hassold and Chiu, 1985), that is, the curve begins to accelerate at ~30–40 years.

The vast majority of all chromosomal non-disjunction events are maternal, not paternal (although for a few specific chromosomes, e.g. chromosome 2, paternal disomies may predominate) (Zaragoza et al., 1998), and nearly 80% of maternal non-disjunctions occur during meiosis I (Antonarakis et al., 1991, 1992, 1993; Sherman et al., 1991; McFadden et al., 1993; Abruzzo and Hassold, 1995). The frequency of MII disomies in comparison with MI disomies varies from chromosome to chromosome (Fisher et al., 1995; Hassold et al., 1995), but it appears that both MI and MII errors increase with advancing maternal age (Yoon et al., 1996). However, there are also data to suggest that all non-disjunction events are the result of errors in MI (Lamb et al., 1996). In either case, we believe it is significant that oocytes are generated only during fetal life and have the same age as the woman bearing them.

Data from other organisms such as yeast and Drosophila have shown that factors causing decreased recombination result in an increase in meiotic non-disjunction and aneuploidy. Analysis of recombination events in human trisomic conceptions has demonstrated a consistent decrease in recombination for maternal non-disjunctive events classified as meiosis I, as well as a change in the chromosomal distribution of these recombination events (Lamb et al., 1996, 1997; Robinson et al., 1998). For MII errors, the results have been less consistent across chromosomes (Bugge et al., 1998), but for trisomy 21, an increase in recombination in pericentromeric regions was described.

These data have led to the hypothesis that the maternal age effect on non-disjunction is a ‘two-hit’ process. In the first hit, the underlying distribution of recombination events per chromosome bivalent, established during fetal life, creates pairs susceptible to non-disjunction, either because of too little or too much pericentromeric recombination. While a young ovary can handle most configurations successfully, older oocytes are likely to undergo non-disjunction, given these less than optimal recombination patterns (Lamb et al., 1996). In the second hit, our hypothesis concerning the role of accumulating mitochondrial DNA mutations addresses the reason for the change in oocyte competence with maternal age.

Chromosomal disjunction, whether in meiosis I or meiosis II, is almost certainly a highly energy-intensive and ATP-dependent process, because the synapsed chromosome pairs (in MI) or sister chromatids (in MII) must be pulled to the opposite ends of the dividing oocyte along the ‘pulley-and-rope’ machinery of the mitotic spindle apparatus (Eichenlaub-Ritter et al., 1996; Eichenlaub-Ritter, 1998). Recent studies have shown that, in vitro, matured oocytes taken from antral follicles of
Oocyte mitochondria and non-disjunction?

Ageing women show spindle abnormalities and problems with chromosome alignment (Battaglia et al., 1996a; Volarcik et al., 1998). Moreover, it has been shown that an increased frequency of oocyte aneuploidies in mice can be related to a specific mitochondrial genotype in the ooplasm (Beermann et al., 1988).

We speculate that mitochondria and mtDNAs in oocytes turn over in order to provide a certain minimum level of energy for oocyte viability. The supposition that mtDNA replicates in the resting oocytes of primordial follicles (currently unverified experimentally) would provide a means by which mutations in mtDNA could arise in otherwise quiescent oocytes and then accumulate over time. Likewise, the surrounding somatic cells, including granulosa precursors, must maintain viability over many years.

The accumulation of mtDNA mutations could have harmful effects on mitochondrial energy production and on overall energy levels in the oocyte. There is only one mitochondrial genome per organelle in oocytes (Michaels et al., 1982; Piko and Taylor, 1987), as opposed to an average of five mtDNAs per organelle in somatic cells (Satoh and Kuroiwa, 1991). Thus, oocytes should be particularly prone to the effects of mtDNA mutations, as mutation in only a single mtDNA molecule could theoretically impair the function of the entire organelle. We also note that the mitochondrial respiratory chain is the single greatest source of free radicals in the body, and that cumulative defects in mtDNA integrity could be intimately associated with damage by reactive oxygen species. Thus, the accumulation of mtDNA mutations might not only affect ATP production directly, but could impair it indirectly and/or secondarily, through the downstream effects of free radicals and oxidative stress on cellular functions (Tarín, 1996; Tarín et al., 1996; 1998).

Problems with the hypothesis

There are at least two key pieces of evidence that do not support this hypothesis. First, there is no evidence that levels of pathogenic mtDNA mutations high enough to cause overt disease can cause karyotypic abnormalities in patient cells. For example, we were unable to detect karyotypic changes in fibroblasts from MERRF patients harbouring >80% mutated mtDNAs (mutation in the tRNA_{Lys} gene), even though it is known that high levels of the MERRF mutation can impair mitochondrial protein synthesis (Masucci et al., 1995). This result implies that either an extremely high level of mutant mtDNAs are required before mitotic non-disjunction occurs (i.e. that non-disjunction is a threshold phenomenon), or that chromosomes can divide well even with reduced ATP values. Of course, evidence...
obtained on mitotic cells may not be applicable to meiotic cells.

A potentially more serious problem for the hypothesis is the fact that women harbouring high levels of pathogenic mtDNA point mutations (usually 50–70% of total mtDNA) are able to have children who are destined to have a serious mitochondrial disorder, yet whose cells are karyotypically normal. This implies that chromosomes in oocytes with severely reduced levels of ATP can still replicate and divide normally. On the other hand, the failure to transmit mtDNA deletions from mother to child, and the extremely high prevalence of spontaneous cytochrome b mutations (and the lack of reported maternally inherited cytochrome b mutations) implies that at least some types of mtDNA mutations interfere with germline or zygotic viability. Examining reproductive histories of women bearing children with mitochondrial disorders for increases in infertility, in spontaneous abortions, or in trisomic offspring might be worthwhile in this context.

**Predictions of the hypothesis**

The hypothesis that mtDNA mutations are associated with trisomies predicts a number of consequences, all of which can be tested experimentally.

First, it predicts that the proportion of mtDNA mutations in oocytes increases as a function of age, irrespective and independent of the presence of aneuploidies in individual germ cells. This issue can be addressed by quantifying mtDNA deletions in oocytes versus age, using methods already described (Chen et al., 1995).

Second, it predicts that the proportion of mtDNA mutations is higher in oocytes harbouring aneuploidies than in normal cells, irrespective of age. This issue can be addressed by performing simultaneous karyotyping and quantitative mtDNA analysis on individual oocytes. In addition, if non-disjunction is due to a high proportion of mtDNA mutations in the oocyte itself, and if this high level of mutation is transmitted to the fetus (i.e. no loss through the bottleneck in early embryogenesis), the hypothesis predicts that the proportion of mtDNA mutations ought to be greater in the somatic cells of trisomic patients or fetuses than in normals, and that patients with trisomies might have mitochondrial diseases at a relatively high frequency.

Third, it implies that mtDNA mutations in oocytes should have detectable biochemical consequences, such as loss of cytochrome c oxidase activity (but see Müller-Höcker et al., 1996). This can be tested by performing respiratory chain histochemistry and immunohistochemistry (Bonilla et al., 1992) on karyotyped oocytes.

Fourth, it also implies that there is mtDNA turnover (presumably by replication) in germ line tissue. This might be able to be verified experimentally via pulse labelling of mtDNAs in vivo (Moraes and Schon, 1995).

Finally, if aneuploidy is primarily the result of energy deficits in the follicular cells, there ought to be a correlation between the level of mtDNA mutations in granulosa cells and the presence of aneuploidy in the oocyte contained within that follicle. This can be tested, for example, by performing in-situ hybridization on sectioned follicles to detect ΔmtDNAs (Mita et al., 1989).

Positive results from experiments of these types would not only support a mitochondrial aetiology for age-related aneuploidies, but might also point the way towards rational approaches to prevention of these devastating birth defects.

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Oocyte mitochondria and non-disjunction?


References


E.A. Schon et al.


