Can we define maternal age as a genetic disease?

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Abstract

Maternal age is strongly associated with a decrease in the probability of achieving pregnancy and the birth of a healthy child. Among current theories of the mechanism of this decrease is the hypothesis that a progressive degeneration of the respiratory capacity of mitochondria in eggs of women of advanced age leads to an energy deficit and consequent secondary effects on the oocyte and developing embryo. Mitochondria are uniquely inherited through the female germ line and these organelles contain DNA sequences that are independent from the genome. It is therefore possible that offspring born to females of advanced age inherit suboptimal mitochondria and that these persist throughout the life of the new being. This could in turn lead to long-term consequences for the offspring of females of advanced age such as a reduced potential lifespan in relation to the age of the mother at conception. In this review and hypothesis, we discuss the evidence relating to this theory and suggest that on this basis the maternal age effect could be classified as an inheritable genetic disease.

Key words: Maternal age, lifespan, mitochondria, epigenetics, mitochondrial inheritance, human reproduction.

Introduction

The beginning of human life may be defined as the moment when sperm and egg fuse to form a zygote with 2 copies of each chromosome. However, in reality this does not mean that all zygotes are equal since the reproductive potential of the zygote and in consequence developing embryo depends on the starting material i.e. the sperm and egg. In many cases, suboptimal gametes lead to developmental arrest of the resulting embryo and failure of implantation. However, even where the formed embryo implants and forms a viable foetus, the health of the resulting offspring is defined by a range of qualitative factors influenced both by the physiological composition of the gametes, and the environment in which they develop.

Which processes can influence the quality of the embryo?

The role of sexual reproduction is to enable the creation of a unique individual through recombination of the genes contained on individual chromosomes, separation of the genomes into two sets of chromosomes during meiosis and the mixing of the male and female sets of chromosomes at fertilisation. This process is a somewhat random event, and can lead to both success (for example a new individual resistant to an environmental pressure) or failure (where a genetic mismatch leads to an individual suffering from genetic disease).

More recent evidence suggests that non-genomic factors also contribute to the health of individuals. Intrinsic factors include the persistence of inherited organelles such as the centrosome or mitochondria in the new being. Extrinsic forces such as environmental conditions during foetal development can also persistently affect the wellbeing of the individual into adult life and may in turn be inherited by their offspring.

The inheritance of organelles

It is well known that each individual inherits a more-or-less equal number of chromosomes from mother and father, the sex chromosomes being the only pair of chromosomes that may be mismatched without drastic consequences. What is less well known is that each individual also inherits a unique

set of organelles from the mother and father separately. The sperm in fact is the sole contributor of the centrosome (Sutovsky and Schatten, 2000). The centrosome is a tubulin body known as a microtubule organising centre and is a necessary catalyst for the formation of the mitotic apparatus (the structure that enables cell divisions to take place). Although centrosomes persist throughout the entire life cycle of all higher animals and are in turn passed to the new being at fertilisation, it is improbable that the centrosome of an adult is a copy of the sperm-derived structure. The centrosome itself contains no DNA, although in some lower animals it has been found to contain RNA (Alliegro et al., 2006). In fact, the DNA coding for centrosomal proteins such as centrin is nuclear (Paoletti et al., 1996) and therefore no extragenomic template exists for the production of new centrosomes. The need for a sperm-derived centrosome at fertilisation therefore is probably inherent to the mechanism of fertilisation itself.

The sperm is not the only gamete to provide a unique structure at fertilisation. In fact the egg is the unique contributor of mitochondria to the embryo. The mitochondrion is the organelle that is principally responsible for generating energy within the cell. In contrast to the centrosome, mitochondria contain extragenomic DNA (termed mtDNA), and replicate as an independent entity throughout the life cycle of the new individual. In fact, mitochondrial DNA is traceable throughout evolution from mother to offspring (Cann et al., 1987). Therefore, in contrast to the centrosome, the mitochondria that humans inherit from their mothers persist throughout the human lifespan and are in turn inherited as conception once again occurs.

The inheritance of an epigenetic program

The DNA of a genome is subjected to modifications that alter the capacity of certain genes to be expressed. This process is termed epigenetic modification and is generally necessary to prevent the overexpression of certain fundamental genes. The best-known epigenetic modification occurs in females. Here, one of the two X-chromosomes is effectively inactivated in order to balance the expression of female genes. The inactive chromosome condenses to form a structure referred to as the Barr body (Barr and Bertram, 1949). Epigenetic modification occurs throughout the genome in the new individual. The epigenetic program is thought to be erased during gametogenesis and early embryogenesis, and a new program imposed (Kelly and Trasler, 2004). However, more recent evidence suggests that some epigenetic modifications are inheritable (Chong and Whitelaw, 2004). Although principal epigenetic modifications are pre-programmed and therefore independent of environment, evidence suggests that some epigenetic modifications are induced by environmental conditions (Walton and Hammond, 1938; Fish et al., 2004). Because the new epigenetic program is imposed during foetal development, the environment of the pregnant mother can influence the epigenetic makeup of the new individual. This may be relevant for example in the case of starvation during pregnancy (Painter et al., 2008). Therefore, external influences during critical phases of development can influence the physiological makeup of newborns, and it is therefore possible that these influences act to determine the lifespan of new individuals.

Could this cause long-term effects?

The evidence above then suggests that a new individual inherits both genomic and extra-genomic genetic contributions at conception, as well as an epigenetic program in relation to the environment the developing foetus experiences during pregnancy. These data suggest that the biological health of the new being is influenced by nuclear and non-nuclear genetics and by environment. Can these factors affect the long-term health of the new individual? Although the answer would appear to be yes, it has been difficult to test the relative contribution of each aspect of the above hypothesis because of the multitude of factors that can affect the lifespan of individuals. The relationship of the parental genomic contribution and the environment of the parents at the moment of conception appears to be well correlated with the health of progeny. Less well established is the role of the parental extra-genomic contribution.

Several lines of evidence suggest that the lifespan of offspring is affected by the age of the parents at conception. In many animal models for example, a correlation has been suggested to exist between the lifespan of parents and their progeny (Lansing, 1947, 1948; Tarin et al., 1998, 2003, 2005; Priest et al., 2002; Garcia-Palomares et al., 2009a, 2009b). In humans, both advanced paternal age (Gavrilov et al., 1997; Gavrilov and Gavrilova, 1997) and maternal age (Bell, 1918; Kemkes-Grottenhaler, 2004; Smith et al., 2009; Wilding et al., 2014) have been suggested to shorten the lifespan of offspring. So what could cause the shortening of lifespan in relation to the age of the parents? Our current hypothesis is that the extra-genomic genetic contribution plays an important role in this effect. The principal extra-genomic genetic contribution to

offspring is in the inheritance of mtDNA from the mother (Wilding et al., 2014). The mitochondrion is the principal non-nuclear organelle in eukaryotic cells. The major role of this organelle is to produce energy in the form of adenosine trisphosphate (ATP) during aerobic respiration. Mitochondria in all cell types are subject to autotoxicity because the mechanism of aerobic respiration involves the production of oxygen free radicals during the reduction of oxygen (Mitchell and Moyle, 1967). These species are highly reactive oxidizing agents and often attack proteins and DNA (mtDNA) within the mitochondria themselves (Oliveira et al., 2010). Damage to proteins may be irrelevant to mitochondria in the long-term, but damage to mtDNA is particularly relevant because mtDNA codes for most of the proteins of the respiratory chain (Iborra et al., 2004). Because mtDNA mutates at high rates (Pesole et al., 1999), any damage is cumulative, suggesting that mitochondrial respiration will lose efficiency over time. Mitochondria in oocytes appear particularly susceptible to age-dependent damage because the 'mitochondrial bottleneck' principle during the formation of primordial oocytes involves the progressive reduction of mitochondrial species to a few copies (Cummins, 2001). These cells then remain quiescent until folliculogenesis is initiated. According to the 'free-radical theory of ageing'; in quiescent cells, the level of damaged mitochondria builds up, eventually causing ageing and death (Linnane et al., 1999). Therefore, even if the level of metabolism in primordial oocytes is minimal, the excessive time span of quiescence (up to 45 years in the human) can still lead to the build-up of damage within the mitochondria. Others and we have previously suggested that the mitochondrial activity of oocytes loses efficiency in relation to the age of the mother (Wilding et al., 2001, 2003, 2005; Van Blerkom, 2004, 2011). This suggests that the mitochondria of ageing females are less efficient at energy production than that of younger individuals. Females pass on 100% of the mitochondria during reproduction, suggesting that advanced maternal, and not paternal age will influence the mtDNA complement in progeny. These data suggest that advanced maternal age would correlate with a shorter lifespan of offspring. In our recent work, we tested this hypothesis by analysing records from a Swedish demographic database (Wilding et al., 2014). We plotted the survival function of lifetime data for 2 centuries of demographic data. The data suggested that the lifespan of progeny did diminish with advanced maternal age. The relative influence of several variables, both intrinsic (such as maternal age) and extrinsic (such as century of birth) was tested. Our data suggested that the most influential intrinsic variables were mothers' lifespan and mothers' age at birth. These data support our hypothesis of the relationship between the inheritance of mtDNA and the lifespan of progeny.

Confounding factors: the environment

Could there be other hypotheses of the relationship between maternal age and the lifespan of offspring? Unfortunately, it is extremely difficult to test single theories due to the undefined nature of 'lifespan'. For example, it could just as easily be argued that older parents cannot adequately care for their progeny, hence the shortening of the lifespan. For example, data suggests that the efficiency of materno-foetal nutrition declines with respect to age, causing gestational complications, premature delivery and low birth weight, and in consequence programming the offspring of mothers of advanced age to a shorter lifespan (Barker et al., 2002; Jolly et al., 2000; Jacobsson et al., 2004; Andersen and Osler, 2004). This could be explained through the epigenetic theory of lifespan, although this hypothesis has not been universally accepted (Cogswell and Yip, 1995; Lawlor et al., 2011; Myrskylä and Fenelon, 2012). Epigenetics suggests that the environment of the foetus causes a modification of the epigenetic program of the developing individual, and this could in turn cause long-term effects on the health of this being. This theory is supported by modern demographic data, particularly in the case of the 'Dutch famine' at the end of the second world war (Painter et al., 2008). In this case study, famine during the second world war caused pregnant mothers to produce smaller offspring. This was expected, however the fact that the children of these progeny were also smaller than normal led to the theory that the condition was inherited. Although full demographic data is not available for this period (i.e. lifespan not concluded), the data lends some weight to an epigenetic theory of the relationship between nutritional efficiency and the program of development of offspring.

Conclusions

Although the moment of conception is seen by many as a renewal of the biological clock, the idea that offspring have a genomic and extra-genomic program of lifespan is compelling. Current data suggests that the natural lifespan of children is influenced more through the mother than the father. Here, we discuss some of the theories that underlie these observations, and suggest that the relationship between the age of the mother and the health of her offspring could be through the inheritance of extra-

genomic genetic material contained within the mitochondria. Since this material degenerates with age, we suggest that maternal age can be defined as a 'genetic disease'. Whether the inheritance of substandard mtDNA is the sole theory to explain the correlation between maternal age and the lifespan of offspring is not known, and the epigenetic theory may also prove to be a profound influence on the lifespan of individuals.

Acknowledgements

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