Diseases Associated with the Mother’s Curse

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The mitochondrion was characterized for years as the energy factory of the cell, but now its role in many more cellular processes is recognized. The mitochondrion and mitochondrial DNA (mtDNA) also possess a set of distinct properties, including maternal inheritance, that creates the Mother’s Curse phenomenon. As mtDNA is inherited from females to all offspring, mutations that are harmful to males tend to accumulate more easily. The Mother’s Curse is associated with various diseases, and has a significant effect on males, in many cases even affecting their reproductive ability. Sometimes, it even leads to reproductive isolation, as in crosses between different populations, the mitochondrial genome cannot cooperate effectively with the nuclear one resulting in a mito-nuclear incompatibility and reduce the fitness of the hybrids. This phenomenon is observed both in the laboratory and in natural populations, and have the potential to influence their evolution and speciation. Therefore, it turns out that the study of mitochondria is an exciting field that finds many applications, including pest control, and it can shed light on the molecular mechanism of several diseases, improving successful diagnosis and therapeutics. Finally, mito-nuclear co-adaptation, paternal leakage, and kin selection are some mechanisms that can mitigate the impact of the Mother’s Curse. Since mitochondria play an important role in many pathways and cellular processes, they are involved in the pathogenesis of many diseases, and thus, the accumulation of mutations in mtDNA can have a serious impact on health and fitness, especially for males, due to its maternal inheritance.

Keywords: mother’s curse ; mitochondrion ; mtDNA ; mito-nuclear incompatibility ; diseases

1. Leber’s Hereditary Optic Neuropathy: The First Record of the MC Effect in Humans

For many years, the manifestation of the MC in humans remained only a theoretical possibility, but recently, Milot et al. (2017) [1] provided the first evidence of the phenomenon occurring in humans for a specific mutation associated with a disease known as Leber’s hereditary optic neuropathy (LHON).

By combining the genetic evidence, historical research, and genealogy data, researchers identified a mutation in mtDNA, T14484C, that escaped the natural selection for about three centuries [1]. This mutation is mapped in a gene that encodes subunits of complex I of the mitochondrial respiratory chain and results in the change of a conserved amino acid [2]. Many years earlier, scientists observed that this mutation was the most common in French-Canadian families with LHON, a maternally inherited disease associated with defects in the optic nerve that finally, leads to severe visual impairment [3]. Leber was also the first to report that LHON primarily affects young adult men [4], and nowadays, it is widely accepted that LHON affects males with a higher frequency than females, due to differences in its penetration [5].

This specific mutation causing LHON (T14484C), appears to have been transferred to Quebec by one of les filles du roy (The King’s Daughters), female immigrants who were sent to the colonies between 1663 and 1673 by King Louis XIV [1][6]. The young woman-carrier of the mutation married and gave birth to 10 children, of whom six were women [1]. Milot et al. (2017) [1] assumed that the MC acted on this case and led to the establishment of this mutation, as the data analysis revealed that male carriers of the mutation had a low level of fitness, compared to the females and male non-carriers. In contrast, the female carriers of the mutation had a higher level of fitness, even in comparison with non-carriers. As a result, despite the negative impact on males, for whom the mutation led to a reduced fitness, the frequency of T14484C increased and finally stabilized in the population, due to selection through females. More specifically, this mutation is found in mtDNA and as this is maternally transmitted, the advantage of this mutation for female carriers led to the positive selection and was not removed by natural selection even though it was associated with a lower level of fitness in males. More specifically, this difference in fitness was surprisingly associated with infant mortality, even though LHON usually emerges many decades later in life [1]. In contrast, female carriers had a higher level of fitness, in comparison with female non-carriers, leading to a stabilization of the mutation in the whole population, as they gave birth to more offspring.

It should be noted that in this study, fitness was measured by the individual's residual reproductive value (RRV) at birth [7]. RRV is a widely used tool in evolutionary and population genetics studies and in simple words, it includes both the current and the expected reproductive output of an individual in the future [8]. In contrast with other measures, such as raw fertility, this methodology has several advantages, such as that it takes into account the age of parents at childbirth and the demographic variation in the population. Then, in the study by Milot et al. (2017), fitness was also adjusted for the population's growth rate, as in previous studies investigating the historical data of human populations [9], in order to obtain reliable and accurate results.

Now, the frequency of the mutation in today's Quebecois is surprisingly high as it is found in approximately 1 in 2000 individuals [10]. Therefore, this study provides a new understanding of the MC in humans and proves that it can cause diseases that affect mainly males.

2. Impact of the MC on the Dimorphic Characters—The Examples of Metabolism and Male Infertility

Sexually dimorphic characteristics are considered those that differ between individuals of different sexes belonging to the same species and they are attributed to evolution through natural selection for the reproductive success [11]. According to the definition of the MC, it is indicated that natural selection can be blind to male-affecting mutations, as selection occurs through females. Therefore, it has been proposed that the main targets of the curse are sexual traits because mutations that affect them have an impact on male fitness and reproductive ability, but generally they have no effect on females or are even beneficial [12][13][14]. In the same way, the selective sieve created by the MC is more likely to act on sexually dimorphic characters [14][15], because the traits that are identical between the two sexes usually function in the same way and mutations affecting them are beneficial or harmful for both males and females. In contrast, mutations that affect male-specific characters and male reproduction are usually neutral for females and more exposed to the MC, continuing to pass onto offspring [13].

The metabolism is considered by scientists to be a dimorphic character, due to the differences between the sexes [15][16]. Females and males exert different metabolic demands [17][18] and as mitochondria, are called the powerhouse of the cell. The mutations on mtDNA usually affect the efficiency of the oxidative phosphorylation and have an impact on the metabolism's efficiency. Regarding the impact of the MC on metabolism, there is some evidence, but it is limited, as most studies do not make comparisons between sexes or study only one sex [19]. Aw et al. (2017) [16] used flies (*Drosophila melanogaster*) of two different lines, with different mtDNA haplotypes, to test how the different haplotypes affected the two sexes, regarding the mitochondrial function and other measured traits (longevity, fertility, etc.). They observed that, generally, males were more affected than females, and males with a specific mitotype also had lower complex I activity and a higher number of mtDNA copies, possibly as a mechanism to ameliorate the effect of the mutations that led to a decrease in the complex I respiration rate. It should also be noted that the two lines were studied on a constant nuclear background. Moreover, Nagarajan-Radha et al. (2020) [19] tested different mtDNA haplotypes in fruit flies and proved that the MC affected the metabolic rate of males, but had no effect on females. In contrast, Novii et al. (2015) [20] conducted a similar study in the past, but with different results. They tested different mtDNA haplotypes in *Drosophila subobscura* to study their effect on the metabolic rate, but they concluded that although a specific sex effect was observed, it could not be clearly stated that it was male-biased. This could potentially be explained by the mechanisms developed to compensate for the impact of the MC and thus mask it [20].

Another characteristic example of the effect of the MC on traits associated with different energy requirements is the work of Carnegie et al. (2021) [15], who studied the wing size. Carnegie et al. (2021) [15] used a rather large mito-nuclear panel of nine mtDNA haplotypes and nine different nuclear genomes, resulting in 81 genotypes examined, to test the hypothesis of the MC effect on the wing size, a sexually dimorphic character that is also associated with the standard metabolic rate and body mass in *D. melanogaster* [21]. The researchers finally found that different combinations of mito-nuclear genomes affected the trait studied, but more importantly, they observed a male-biased effect, as mtDNA created a greater variance for males. Thus, they concluded that their hypothesis was proven [15].

In the same perspective, females and males exert different metabolic demands [17][18], and this is reflected intensively in their reproductive systems. The male reproductive system exerts many differences from the female reproductive system and it has higher energy requirements than the females. Mammalian spermatozoa contain many mitochondria in a region called the midpiece, and use ATP for movement to traverse the female reproductive tract and reach the ovum; in addition, ATP is essential for processes required for fertilization, such as capacitation, hyperactivation, and the acrosome reaction [22][23][24]. Therefore, the MC can contribute to male infertility [13][25], as the mutations in mtDNA that alter the ATP production efficiency affect a male's reproductive ability and, at the same time, have a mild impact on a female's

reproductive system that has lower energy requirements. Innocenti et al. (2011) [14] studied some mitochondrial variants in *D. melanogaster* and observed important differences between the two sexes. More specifically, the variants induced changes in the gene expression of males, affecting approximately 10% of all transcripts, and interestingly, nuclear genes were also affected as the two genomes interact to achieve the proper function of organisms. It was also highlighted that most of the transcripts that were affected, they exhibited a male-biased expression, and they were mainly expressed in the male reproductive tissues, such as the testes [14]. Thus, with this mechanism, it is very likely that the accumulation of the mtDNA mutations affects the reproductive fitness of males. There are also several other studies associating the mitochondrial variants with male reproduction. Dowling et al. (2007) [26] reported that mutations in the cytoplasmic genes affected two traits that are important for a male's reproductive success in the seed beetle (*Callosobruchus maculatus*): the sperm viability, and length. Other examples that provide evidence for the effect of the MC on the male fertilization capacity can be found in studies involving many different animals. A study on the European brown hare (*Lepus europaeus*) [25] observed that the insertion of a remote population with a different mtDNA haplotype in a captive colony led to a decrease in male fertility, whereas in the rooster (*Gallus domesticus*), researchers found that sperm mobility was affected negatively by the mitochondrial function and a specific mitochondrial variation [27]. In *Drosophila*, some studies also associate the mitochondrial haplotypes with male infertility [28]. As Patel et al. (2016) [29] proved, an mtDNA hypomorph of cytochrome c oxidase subunit II decreases male fertility, but at the same time, it does not affect females. Regarding humans, several studies also associate the variants in mtDNA with an effect on a male's reproductive ability, leading mainly to a decrease in sperm motility [30][31][32][33][34][35], as it is the main sperm parameter directly associated with large energy requirements.

At this point, the role of the environment that affects the mito-nuclear interactions [36][37] and thus, the MC effect should also be considered. Montooth et al. (2019) [38] tested some flies' genotypes using different combinations between mtDNA haplotypes and nuclear genomes. They reported that a specific mito-nuclear incompatible genotype caused male infertility but only when the males developed at high temperatures. More interestingly, the phenotype could be saved by alterations in diet, indicating the important contribution of the environment to the MC manifestation. M. F. Camus et al. (2020) [37] also suggested that there is a link between the mtDNA variation, male feeding behavior, and reproductive ability, while Wolff et al. (2016) [39] reported that the environment and specifically the thermal gradient, can play a role in male fertility in fruit flies. Therefore, further research and experiments are strongly recommended to understand the complex interactions between the genotype and environment.

Finally, it should be noted that there may be a particular exception regarding the reproductive investment in some marine species, as there are female fish that produce several thousand or even millions of eggs, indicating an equal or even greater energy investment for reproduction with males. An extreme example is that of a large dolphinfish (*Coryphaena hippurus*) that is estimated to produce approximately 100 million eggs per year [40], but in general, the ovaries are considered very active organs in fish and consume large amounts of energy for the egg production [41]. In these cases, it is possible that the MC does not lead to such a great impact as the mutations that affect the OXPHOS efficiency, and the energy production affects equally females and males, and potentially even greater for females, though it is difficult to estimate with a high accuracy the energy investment for reproduction in both sexes [42]. Therefore, this can potentially prevent the accumulation of such mutations leading to male infertility. However, the number of studies on male infertility in fish species, especially regarding mtDNA mutations, in contrast with studies on mammals, as referred to above, is very limited or even scarce at all, in order to draw reliable conclusions. In conclusion, more research is needed in this particular field to assess the impact of the MC on male infertility for fish species.

3. MC and the Aging of Males

Aging is a complex process that is associated with some important hallmarks, including the genomic instability, mitochondrial dysfunction, telomere shortening, epigenetic alterations, etc. [43][44]. However, aging is also a process that exerts large differences between the two sexes, since females tend to live longer than males, although they are considered to have a poorer health associated with a greater comorbidity [44][45][46][47]. Taking into account the key role of mitochondria and the mitochondrial genome in aging [48][49][50], as there is an increase in the amount of evidence linking the mtDNA variants with age-related diseases [51], and highlighting the role of mtDNA in the regulation of the lifespan [52] [53], several studies indicate that the MC effect can contribute to the longevity gap observed between the sexes.

M. Florencia Camus et al. (2012) [54] screened male and female fruit flies (*D. melanogaster*) with different mitochondrial haplotypes to study the mitochondrial variants and their effect on the longevity traits. They observed that due to the maternal inheritance of mtDNA, numerous mutations in the mitochondrial genome have accumulated, that affect the aging in males but not in females, providing indications for a sex-specific selective sieve. However, the impact of these mutations on the efficiency of the OXPHOS system and in terms of ATP production was not investigated. It is also interesting that Milot et al. (2017) [1], except for proving the MC role in the occurrence of LHON in the Canadian

population, among other findings, highlight that the mutation that causes LHON also contributes to a shorter lifespan for men, as it is associated with infant mortality. Wolff and Gemmell (2013) [55], based on previous findings, also indicate that the mtDNA variants and maternal inheritance of mtDNA can lead to the aging asymmetry observed between the two sexes.

Furthermore, following previous studies that show the important role of the environment in the manifestation of male infertility, there is also evidence linking sex-biased aging with environmental factors. Aw et al. (2017) [16] used two *Drosophila* lines with different mitotypes and fed them four diets that differed in the protein to carbohydrate ratios. Then, they tried to explore the mitochondrial genotype-by-diet interactions by measuring four traits, including longevity. They observed an impact of the sex-specific mitotypes, and more specifically, the males with a specific haplotype that ate a specific diet (with higher protein ratios) had a decreased longevity. There are also some other studies indicating that the variation in the mtDNA can have diet-dependent effects on longevity [56][57], but they may not compare the differences between sexes or they can lead to contradicting results, due to the insertion of the new parameters studied. Therefore, no clear conclusions can be drawn about the association between the MC, diet and aging, but all of the above findings highlight the effect of the environment on mito-nuclear interactions and a possible association between the MC and male aging.

Though a comprehensive understanding of the effect of the MC in aging is limited, according to one hypothesis, it can be associated with sexual dimorphism [54] and more specifically, the differences in energy requirements and metabolism between the sexes [13][58]. Males exert a higher basal metabolic rate [13], but since selection occurs through females, the mitochondria with mtDNA mutations have difficulty coping with the higher metabolic demands of males, and therefore are more exposed to dysfunction and damage [13]. Mitochondrial dysfunction is one of the hallmarks associated with aging [43], and thus, can contribute to a different longevity observed between the sexes. However, more evidence is required to support this theory. Furthermore, leaving aside the different metabolic requirements between the two sexes, another link can exist between aging and the MC that goes through metabolism. Studies in many experimental models associate metabolism and energy utilization with the aging process [59][60][61]. More specifically, dietary restriction [62][63], and the availability of specific nutrients, have been correlated with the metabolic alterations and finally an effect on the lifespan [59]. Therefore, as the MC has been associated with an impact on the metabolism, as explained above, maybe this male-biased effect can also negatively affect the longevity of males, due to the metabolism's contribution, as well as the mitochondrial's dysfunction to aging.

References

1. Milot, E.; Moreau, C.; Gagnon, A.; Cohen, A.A.; Brais, B.; Labuda, D. Mother's Curse Neutralizes Natural Selection against a Human Genetic Disease over Three Centuries. Nat. Ecol. Evol. 2017, 1, 1400–1406.
2. MacMillan, C.; Johns, T.A.; Fu, K.; Shoubridge, E.A. Predominance of the T14484C Mutation in French-Canadian Families with Leber Hereditary Optic Neuropathy Is Due to a Founder Effect. Am. J. Hum. Genet. 2000, 66, 332–335.
3. Macmillan, C.; Kirkham, T.; Fu, K.; Allison, V.; Andermann, E.; Chitayat, D.; Fortier, D.; Gans, M.; Hare, H.; Quercia, N.; et al. Pedigree Analysis of French Canadian Families with T14484C Leber's Hereditary Optic Neuropathy. Neurology 1998, 50, 417–422.
4. Leber, T. Ueber Hereditäre Und Congenital-Angelegte Sehnervenleiden. Albrecht Von Graefes Arch. Für Ophthalmol. 1871, 17, 249–291.
5. Hage, R.; Vignal-Clermont, C. Leber Hereditary Optic Neuropathy: Review of Treatment and Management. Front. Neurol. 2021, 12, 651639.
6. Laberge, A.M.; Jomphe, M.; Houde, L.; Vézina, H.; Tremblay, M.; Desjardins, B.; Labuda, D.; St-Hilaire, M.; Macmillan, C.; Shoubridge, E.A.; et al. A "Fille Du Roy" Introduced the T14484C Leber Hereditary Optic Neuropathy Mutation in French Canadians. Am. J. Hum. Genet. 2005, 77, 313–317.
7. Moorad, J.A. Individual Fitness and Phenotypic Selection in Age-Structured Populations with Constant Growth Rates. Ecology 2014, 95, 1087–1095.
8. Delaney, D.M.; Hoekstra, L.A.; Janzen, F.J. Age Predicts Risky Investment Better Than Residual Reproductive Value. Am. Nat. 2021, 197, 461–472.
9. Moorad, J.A. A Demographic Transition Altered the Strength of Selection for Fitness and Age-Specific Survival and Fertility in a 19th Century American Population. Evolution 2013, 67, 1622–1634.
10. Gemmell, N. The Curse of the Filles Du Roy. Nat. Ecol. Evol. 2017, 1, 1228–1229.

11. Moore, A.J. The Evolution of Sexual Dimorphism by Sexual Selection: The Separate Effects of Intrasexual Selection and Intersexual Selection. Evolution 1990, 44, 315–331.
12. Gemmell, N.J.; Metcalf, V.J.; Allendorf, F.W. Mother's Curse: The Effect of MtDNA on Individual Fitness and Population Viability. Trends Ecol. Evol. 2004, 19, 238–244.
13. Beekman, M.; Dowling, D.K.; Aanen, D.K. The Costs of Being Male: Are There Sex-Specific Effects of Uniparental Mitochondrial Inheritance? Philos. Trans. R. Soc. Lond. B Biol. Sci. 2014, 369, 20130440.
14. Innocenti, P.; Morrow, E.H.; Dowling, D.K. Experimental Evidence Supports a Sex-Specific Selective Sieve in Mitochondrial Genome Evolution. Science 2011, 332, 845–848.
15. Carnegie, L.; Reuter, M.; Fowler, K.; Lane, N.; Camus, M.F. Mother's Curse Is Pervasive across a Large Mitonuclear Drosophila Panel. Evol. Lett. 2021, 5, 230–239.
16. Aw, W.C.; Garvin, M.R.; Melvin, R.G.; Ballard, J.W.O. Sex-Specific Influences of MtDNA Mitotype and Diet on Mitochondrial Functions and Physiological Traits in Drosophila Melanogaster. PLoS ONE 2017, 12, e0187554.
17. Geer, E.B.; Shen, W. Gender Differences in Insulin Resistance, Body Composition, and Energy Balance. Gend. Med. 2009, 6 (Suppl. 1), 60–75.
18. Wu, B.N.; O'Sullivan, A.J. Sex Differences in Energy Metabolism Need to Be Considered with Lifestyle Modifications in Humans. J. Nutr. Metab. 2011, 2011, 391809.
19. Nagarajan-Radha, V.; Aitkenhead, I.; Clancy, D.J.; Chown, S.L.; Dowling, D.K. Sex-Specific Effects of Mitochondrial Haplotype on Metabolic Rate in Drosophila Melanogaster Support Predictions of the Mother's Curse Hypothesis. Philos. Trans. R. Soc. B Biol Sci 2020, 375, 20190178.
20. Novičić, Z.K.; Immonen, E.; Jelić, M.; Anelković, M.; Stamenković-Radak, M.; Arnqvist, G. Within-Population Genetic Effects of MtDNA on Metabolic Rate in Drosophila Subobscura. J. Evol. Biol. 2015, 28, 338–346.
21. Videlier, M.; Careau, V.; Wilson, A.J.; Rundle, H.D. Quantifying Selection on Standard Metabolic Rate and Body Mass in Drosophila Melanogaster. Evolution 2021, 75, 130–140.
22. Visconti, P.E. Sperm Bioenergetics in a Nutshell. Biol. Reprod. 2012, 87, 72–73.
23. Du Plessis, S.S.; Agarwal, A.; Mohanty, G.; Van Der Linde, M. Oxidative Phosphorylation versus Glycolysis: What Fuel Do Spermatozoa Use? Asian J. Androl. 2015, 17, 230–235.
24. Misro, M.M.; Ramya, T. Fuel/Energy Sources of Spermatozoa. In Male Infertility: Contemporary Clinical Approaches, Andrology, ART and Antioxidants; Springer: New York, NY, USA, 2012; pp. 209–223. ISBN 9781461433354.
25. Smith, S.; Turbill, C.; Suchentrunk, F. Introducing Mother's Curse: Low Male Fertility Associated with an Imported MtDNA Haplotype in a Captive Colony of Brown Hares. Mol. Ecol. 2010, 19, 36–43.
26. Dowling, D.K.; Nowostawski, A.L.; Arnqvist, G. Effects of Cytoplasmic Genes on Sperm Viability and Sperm Morphology in a Seed Beetle: Implications for Sperm Competition Theory? J. Evol. Biol. 2007, 20, 358–368.
27. Froman, D.P.; Kirby, J.D. Sperm Mobility: Phenotype in Roosters (Gallus domesticus) Determined by Mitochondrial Function. Biol. Reprod. 2005, 72, 562–567.
28. Yee, W.K.W.; Sutton, K.L.; Dowling, D.K. In Vivo Male Fertility Is Affected by Naturally Occurring Mitochondrial Haplotypes. Curr. Biol. 2013, 23, R55–R56.
29. Patel, M.R.; Miriyala, G.K.; Littleton, A.J.; Yang, H.; Trinh, K.; Young, J.M.; Kennedy, S.R.; Yamashita, Y.M.; Pallanck, L.J.; Malik, H.S. A Mitochondrial DNA Hypomorph of Cytochrome Oxidase Specifically Impairs Male Fertility in Drosophila Melanogaster. elife 2016, 5, e16923.
30. Shamsi, M.B.; Kumar, R.; Bhatt, A.; Bamezai, R.N.K.; Kumar, R.; Gupta, N.P.; Das, T.K.; Dada, R. Mitochondrial DNA Mutations in Etiopathogenesis of Male Infertility. Indian J. Urol. 2008, 24, 150–154.
31. Holyoake, A.J.; McHugh, P.; Wu, M.; O'Carroll, S.; Benny, P.; Sin, I.L.; Sin, F.Y.T. High Incidence of Single Nucleotide Substitutions in the Mitochondrial Genome Is Associated with Poor Semen Parameters in Men. Int. J. Androl. 2001, 24, 175–182.
32. St. John, J.C.; Jokhi, R.P.; Barratt, C.L.R. The Impact of Mitochondrial Genetics on Male Infertility. Int. J. Androl. 2005, 28, 65–73.
33. Al Zoubi, M.S.; Al-Talafha, A.M.; Al Sharu, E.; Al-Trad, B.; Alzu'Bi, A.; AbuAlarjah, M.I.; Shehab, Q.; Alsmadi, M.; Al-Batayneh, K.M. Correlation of Sperm Mitochondrial DNA 7345 Bp and 7599 Bp Deletions with Asthenozoospermia in Jordanian Population. J. Reprod. Infertil. 2021, 22, 165–172.
34. Karimian, M.; Babaei, F. Large-Scale MtDNA Deletions as Genetic Biomarkers for Susceptibility to Male Infertility: A Systematic Review and Meta-Analysis. Int. J. Biol. Macromol. 2020, 158, 85–93.

35. Dzudzor, B.; Bimah, B.; Amarh, V.; Ocloo, A. Sperm Parameters and Mitochondrial DNA Sequence Variants among Patients at a Fertility Clinic in Ghana. PLoS ONE 2021, 16, e0252923.

36. Zhu, C.T.; Ingelmo, P.; Rand, D.M. G×G×E for Lifespan in Drosophila: Mitochondrial, Nuclear, and Dietary Interactions That Modify Longevity. PLoS Genet. 2014, 10, e1004354.

37. Camus, M.F.; Moore, J.; Reuter, M. Nutritional Geometry of Mitochondrial Genetic Effects on Male Fertility. Biol. Lett. 2020, 16, 20190891.

38. Montooth, K.L.; Dhawanjewar, A.S.; Meiklejohn, C.D. Temperature-Sensitive Reproduction and the Physiological and Evolutionary Potential for Mother's Curse. Integr. Comp. Biol. 2019, 59, 890–899.

39. Wolff, J.N.; Tompkins, D.M.; Gemmell, N.J.; Dowling, D.K. Mitonuclear Interactions, MtDNA-Mediated Thermal Plasticity, and Implications for the Trojan Female Technique for Pest Control. Sci. Rep. 2016, 6, 30016.

40. McBride, R.S.; Snodgrass, D.J.G.; Adams, D.H.; Rider, S.J.; Colvocoresses, J.A. An Indeterminate Model to Estimate Egg Production of the Highly Iteroparous and Fecund Fish, Dolphinfish (Coryphaena hippurus). Bull. Mar. Sci. 2012, 88, 283–303.

41. Lubzens, E.; Young, G.; Bobe, J.; Cerdà, J. Oogenesis in Teleosts: How Eggs Are Formed. Gen. Comp. Endocrinol. 2010, 165, 367–389.

42. Hayward, A.; Gillooly, J.F. The Cost of Sex: Quantifying Energetic Investment in Gamete Production by Males and Females. PLoS ONE 2011, 6, e16557.

43. López-Otín, C.; Blasco, M.A.; Partridge, L.; Serrano, M.; Kroemer, G. The Hallmarks of Aging. Cell 2013, 153, 1194–1217.

44. Hägg, S.; Jylhävä, J. Sex Differences in Biological Aging with a Focus on Human Studies. elife 2021, 10, 936–944.

45. Gordon, E.H.; Hubbard, R.E. Do Sex Differences in Chronic Disease Underpin the Sex-Frailty Paradox? Mech. Ageing Dev. 2019, 179, 44–50.

46. Gordon, E.H.; Peel, N.M.; Samanta, M.; Theou, O.; Howlett, S.E.; Hubbard, R.E. Sex Differences in Frailty: A Systematic Review and Meta-Analysis. Exp. Gerontol. 2017, 89, 30–40.

47. Austad, S.N.; Fischer, K.E. Sex Differences in Lifespan. Cell Metab. 2016, 23, 1022–1033.

48. Sun, N.; Youle, R.J.; Finkel, T. The Mitochondrial Basis of Aging. Mol. Cell 2016, 61, 654–666.

49. Chistiakov, D.A.; Sobenin, I.A.; Revin, V.V.; Orekhov, A.N.; Bobryshev, Y.V. Mitochondrial Aging and Age-Related Dysfunction of Mitochondria. Biomed Res. Int. 2014, 2014, 238463.

50. Lionaki, E.; Gkikas, I.; Daskalaki, I.; Ioannidi, M.-K.; Klapa, M.I.; Tavernarakis, N. Mitochondrial Protein Import Determines Lifespan through Metabolic Reprogramming and de Novo Serine Biosynthesis. Nat. Commun. 2022, 13, 651.

51. Zapico, S.C.; Ubelaker, D.H. MtDNA Mutations and Their Role in Aging, Diseases and Forensic Sciences. Aging Dis. 2013, 4, 364–380.

52. Sebastián, D.; Palacín, M.; Zorzano, A. Mitochondrial Dynamics: Coupling Mitochondrial Fitness with Healthy Aging. Trends Mol. Med. 2017, 23, 201–215.

53. Akbari, M.; Kirkwood, T.B.L.; Bohr, V.A. Mitochondria in the Signaling Pathways That Control Longevity and Health Span. Ageing Res. Rev. 2019, 54, 100940.

54. Camus, M.F.; Clancy, D.J.; Dowling, D.K. Mitochondria, Maternal Inheritance, and Male Aging. Curr. Biol. 2012, 22, 1717–1721.

55. Wolff, J.N.; Gemmell, N.J. Mitochondria, Maternal Inheritance, and Asymmetric Fitness: Why Males Die Younger. BioEssays 2013, 35, 93–99.

56. Camus, M.F.; O'Leary, M.; Reuter, M.; Lane, N. Impact of Mitonuclear Interactions on Life-History Responses to Diet. Philos. Trans. R. Soc. Lond. B Biol. Sci. 2020, 375, 20190416.

57. Nagarajan-Radha, V.; Rapkin, J.; Hunt, J.; Dowling, D.K. Interactions between Mitochondrial Haplotype and Dietary Macronutrient Ratios Confer Sex-Specific Effects on Longevity in Drosophila Melanogaster. J. Gerontol. A Biol. Sci. Med. Sci. 2019, 74, 1573–1581.

58. Flanagan, B.A.; Li, N.; Edmands, S. Mitonuclear Interactions Alter Sex-Specific Longevity in a Species without Sex Chromosomes. Proc. R. Soc. B 2021, 288, 20211813.

59. Finkel, T. The Metabolic Regulation of Aging. Nat. Med. 2015, 21, 1416–1423.

60. Fontana, L.; Partridge, L. Promoting Health and Longevity through Diet: From Model Organisms to Humans. Cell 2015, 161, 106–118.
61. Azzu, V.; Valencak, T.G. Energy Metabolism and Ageing in the Mouse: A Mini-Review. Gerontology 2017, 63, 327–336.
62. Weir, H.J.; Yao, P.; Huynh, F.K.; Escoubas, C.C.; Goncalves, R.L.; Burkewitz, K.; Laboy, R.; Hirschey, M.D.; Mair, W.B. Dietary Restriction and AMPK Increase Lifespan via Mitochondrial Network and Peroxisome Remodeling. Cell Metab. 2017, 26, 884–896.e5.
63. Anton, S.; Leeuwenburgh, C. Fasting or Caloric Restriction for Healthy Aging. Exp. Gerontol. 2013, 48, 1003–1005.