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Maternal inheritance, sexual conflict and the maladapted male

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Females differ from males in transmitting not only nuclear genes but also cytoplasmic genetic elements (CGEs), including DNA in mitochondria, chloroplasts and microorganisms that are present in the cell. Until recently, evolutionary research has adopted a nucleocentric approach in which organelles have been viewed as subservient energy suppliers. In this article, we propose that a more equitable view of nuclear genes and organelle genomes will lead to a better understanding of the dynamics of sexual selection and the constraints on male adaptation. Maternal inheritance of CGEs intensifies sexually-antagonistic coevolution and provides a parsimonious explanation for the relatively high frequency in males of such apparently maladaptive traits as infertility, homosexuality and baldness.

Introduction

At its most basic level, gender is defined by the relative size of the gametes. Females produce few, large and 'costly' eggs, whereas males produce many small, 'inexpensive' sperm. This differential investment in gametes has been identified as a fundamental force driving the evolution of divergent mating tactics in males and females [1], and as a source of nucleocytoplasmic conflict (see Glossary) over optimal sex ratio [2–4]. In most plants and animals, anisogamy is coupled with strictly maternal inheritance of organelles and other genetic elements in the cytoplasm [5]. Males are thus a dead-end for cellular organelles, such as mitochondria and chloroplasts and for cellular endosymbionts, such as protists, bacteria and viruses. Selection on cytoplasmic genetic elements (CGEs) should therefore favour variants capable of biasing sex ratio towards females. With males becoming rare, their average reproductive success increases. Selection on biparentally-inherited, nuclear genes should then promote mutations that restore maleness, setting in motion an evolutionary arms race over optimal sex ratio [3,4]. Support for the importance of such nucleocytoplasmic conflict is provided by a proliferation of studies demonstrating male-killing or feminizing by cellular endosymbionts in arthropods and mitochondria in flowering plants (Box 1). In this article, we propose an expanded domain in which to consider the implications of uniparental inheritance of CGEs. We hypothesize that, in addition to generating conflict over sex ratio, maternal inheritance of CGEs intensifies sexually antagonistic coevolution and constrains the capacity of males to evolve in response to both natural and sexual selection.

Mitochondria and selfish Y-chromosomes: inexorably at odds

Because of their diametrically opposed, uniparental modes of inheritance, CGEs and genes on the Y-chromosome are in direct conflict over sex ratio. Hurst [6] has proposed that, because of strict paternal inheritance, the non-recombining region of the Y-chromosome serves as an attractor for the evolution of selfish growth factors (Y-SGFs) in live-bearing species. Indeed, in several mammals, Y-linked gene expression results in male embryos that develop and implant faster than females [7,8]. By triggering uterine changes that inhibit subsequent implantation by slower developing blastocysts, Y-SGFs promote their own transmission by causing mothers to differentially abort XX embryos. It has been hypothesized that such male-biasing effects promote the evolution of inhibitory factors or counterbalancing growth factors on the X-chromosome [9]. We suggest that sex-ratio conflict is likely to be even more intense between Y-SGFs and mitochondria. Expression of Y-SGFs not only spells non-transmission for mitochondria in that particular embryo, but can also lead to elimination of clonally-related mitochondrial lineages in aborted XX siblings.

Direct evidence that mammalian mitochondria can respond adaptively to this threat by killing or feminizing males is currently lacking. Indeed, the size of the vertebrate mitochondrial genome has been viewed as a constraint on its capacity to influence complex phenotypic traits such as sex determination [4]. However,

Glossary

Anisogamy: refers to reproduction by the union of dissimilar gametes. Most commonly, gamete types differ in size and motility.
Nucleocytoplasmic conflict: involves antagonism between nuclear and cytoplasmic genes that occurs as a consequence of their differing modes of transmission.
Apoptosis: is a cellular process involving a genetically programmed series of events leading to cell death.
Penetrance: pertains to the failure of some individuals with a mutant genotype to express the associated mutant phenotype. Incomplete penetrance usually results from chance influences or modifiers in the genetic background.
Gynodioecious: populations occur in some plant species and consist of a mixture of individuals that produce flowers having only female functional reproductive organs and others that produce flowers with both male and female functional reproductive organs.

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Box 1. Cytoplasmic sex-ratio distorters in invertebrates and plants

Cellular endosymbionts

Sex-ratio distortion by cellular endosymbionts is widespread in invertebrates and is achieved through a variety of mechanisms by a diversity of CGEs. The most common endosymbionts are intracellular bacteria in the genus, *Wolbachia*, that infect an estimated 76% of insect species, and also infect some nematodes, crustaceans and arachnids [48]. *Wolbachia* manipulate the sex ratio of their host by either killing male embryos, feminizing diploid males or, in haplo-diploid species, inducing parthenogenesis [48]. In the absence of nuclear male-restorer alleles, selection can result in greater frequencies of CGEs and extremely female-biased populations, with dramatic consequences for sexual selection, such as sex-role-reversed mating systems [49]. Other cellular endosymbionts, such as *Rickettsia* and *Spiroplasma* bacteria, and Microsporidia, which are unicellular eukaryotes, have also been implicated in male killing and feminization.

Feminizing mitochondria in angiosperms

Not surprisingly, given their endosymbiotic origin, cellular organelles can also manipulate sex ratio. In flowering plants, mitochondrial mutants convert hermaphrodites into females by undermining their ability to produce male gametes. Manifestations of male sterility range from complete absence of male sex organs to production of dysfunctional pollen. Such cytoplasmic male sterility (CMS) results in a gynodioecious mating system, in which hermaphrodites co-occur with females. In nearly all cases in which a likely causative agent has been identified, CMS is linked to rearrangements in the mitochondrial genome. Although most mitochondrial variants involved in CMS show little sequence homology, they have 'chimeric' open reading frames (ORFs) that are often closely linked to and co-transcribed with essential mitochondrial genes [50].

Feminization of hermaphrodites is generally advantageous for mitochondria, because reallocation of plant resources from male to female function should increase ovule production and/or female survival, thereby enhancing mtDNA transmission. As predicted by nucleocytoplasmic-conflict theory, many species exhibiting CMS harbor nuclear restorers that act by targeted elimination of the feminizing mitochondrial ORF or, more commonly, by interference with its post-transcriptional expression [50].

experimental studies of mitochondrial effects on ageing [10] and nervous system development [11] demonstrate that mitochondrial DNA (mtDNA) variation can have profound phenotypic consequences, resulting from extensive crosstalk between nuclear and mitochondrial genomes. In mice, expression of as many as 200 nuclear genes can be modified by mtDNA haplotype [12]. The mitochondrion has been described as a 'receiver/integrator organelle' that can '…respond to energy demands as well as to cell growth, cell death and a variety of physiological stimuli and stresses' by signalling pathways involving protein kinases, transcription factors, regulatory Ca^{2+} fluxes and receptors for cytokines, hormones and growth factors [13]. Moreover, it is increasingly evident that mitochondria have a pivotal role in initiating apoptosis: release of apoptogenic, mitochondrial proteins activates cysteine-aspartate proteases and endonucleases, resulting in cell self-digestion and nuclear-DNA fragmentation [14]. These findings, together with the strong link between embryonic metabolic rate and sex determination in mammals [8], suggest plausible mechanisms through which mitochondria could block male-determining, developmental processes. For example, in response to an increased metabolic rate in the early-stage embryo, mitochondria could kill or feminize males by initiating apoptosis in important cell lineages.

Compared with the larger genomes of bacteria and plant mitochondria, animal mitochondrial genomes are likely to be more constrained in their capacity to influence sex ratio. Nonetheless, in the light of the new evidence of mitochondrial involvement in complex fitness traits in mice and humans, we suggest that mutations capable of biasing sex ratio could periodically occur in animal mtDNA. Investigation of possible involvement of mitochondria in feminization seems particularly warranted in the case of two phenomena which have defied explanation based on classical, mendelian genetics. The first phenomenon involves the occurrence of fertile, heterogametic XY* females in *Akodon* field mice (Box 2). Despite extensive research, the mechanism responsible for feminization of XY* individuals has not been determined [15]. We suggest that applying the principle of *cui bono* (or good for whom) might prove fruitful in this case. Among the potential causal agents, mitochondrial genes have the most to gain from a process that converts XY* males to females, thereby harnessing selfish growth factors that would otherwise impede mitochondrial transmission. The second phenomenon is that of homosexuality and gender identity among human males. Twin and pedigree studies indicate that sexual orientation in males is influenced by maternally-inherited factors [16]. However, attempts to link male homosexuality to genes on the X-chromosome have proved equivocal [17]. Expanding on an idea proposed by Hurst and Haig (see Ref. [18]), Sykes [19] has proposed that male homosexuality might stem from incomplete penetrance of a mitochondrial haplotype selected for its ability to kill males during intrauterine development. Consistent with this hypothesis is the finding that maternal aunts significantly outnumber maternal uncles in both homosexual [20] and transsexual men [21]. Such female bias is not evident in the males' paternal relatives or in the relatives of lesbians and female transsexuals. This hypothesis of mitochondrial involvement in male homosexuality is testable, given the relative ease with which mitochondrial genomes can now be sequenced.

Uniparental inheritance of cytoplasmic genes: implications for antagonistic coevolution between the sexes

DNA evidence of multiple paternity in vertebrate and invertebrate species has established that polyandrous mating systems are the norm rather than the exception. Theory predicts that the mating system is a key determinant of the intensity of antagonistic coevolution between the sexes [22]. With strict monogamy, male and female reproductive interests coincide, and selection favours cooperative males that maximize their mates' lifetime reproductive success. By contrast, when both sexes copulate with multiple partners, conflicts occur over mating frequency, timing and pattern of fertilization,

Box 2. Feminization of XY males in *Akodon*

In at least nine species of the South American rodent genus, *Akodon*, heterogametic XY* females occur together with normal XX females and XY males [51]. Although feminization has been attributed to an 'inactivation mutation' on the Y*-chromosome [52], sequencing and restriction fragment length polymorphism (RFLP) studies of *Sry* – the primary male-determining gene in mammals – have not detected any within-species differences between XY and XY* individuals [15,51]. Both Y- and Y*-chromosomes possess multiple copies of the *Sry* locus, and the male-specific zinc finger locus, *Zfy* [15]. XY* embryos exhibit accelerated pre-implantation growth rates compared with both XX and XY embryos [53], suggesting that selfish growth factors might be particularly active on Y*-chromosomes. This faster growth rate of XY* embryos accounts for the Y*-chromosome transmission advantage and the bias towards all-female litters in the offspring of heterogametic females [53]. Although one-quarter of embryos produced by XY* females have a Y*Y genotype and are inviable, mathematical models indicate that the Y*-transmission advantage and the greater lifetime reproductive rate of XY* females are sufficient for the Y*-chromosome to invade and persist at low-to-intermediate frequencies in natural populations [52] (Figure I).

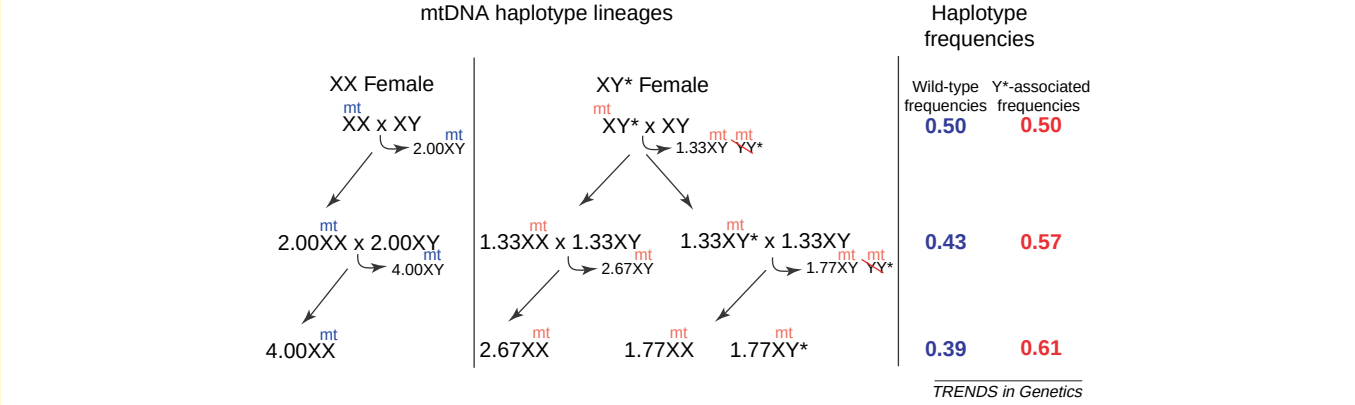

Figure I. MtDNA haplotype and frequencies. Feminization in *Akodon* has major fitness consequences for its associated mtDNA haplotype. The figure (modified from Ref. [52]) shows a change in wild-type haplotype frequency and XY*-associated haplotype frequency across two generations (assuming a litter size of four). Note that straight arrows represent continuing haplotype lineages whereas curved arrows denote offspring production in which mtDNA is not transmitted. Although YY* embryos are inviable, XY* females give birth to as many pups as XX females [54], as a consequence of reproductive compensation (over-production of oocytes). Owing to feminization, two-thirds of the offspring produced by XY* females are daughters and therefore transmit mitochondria, compared with only one-half of XX females' progeny. Consequently, mtDNA haplotypes in XY* mothers are transmitted to 1.33 times as many daughters as those in XX mothers. Using recursion equations, Hoekstra [52] showed that an XY*-associated mitochondrial haplotype rapidly spreads to fixation.

relative parental effort, female re-mating behaviour, female reproductive rate and clutch size [23]. Such sexual conflict is frequently manifested at the post-copulatory stage in the female reproductive tract as a 'tug-of-war' between male offensive and defensive strategies for monopolizing access to the female's eggs (e.g. toxic peptides in seminal fluid that influence brain function in *Drosophila* females) and resistance by the female to male manipulation of her physiology and male control of her reproductive options [23].

Maternal inheritance of CGEs has implications for the relationship between sexual selection and sexual conflict that are only now being recognized [24]. Critics of sexual-conflict theory argue that females gain a net reproductive benefit by mating with manipulative males because the direct costs they suffer are outweighed by the production of 'sexy' (i.e. manipulative) sons [25]. Apparent male–female conflict could thus form part of a reproductive interaction whose net coevolutionary effect is cooperative and therefore in accordance with traditional sexual-selection theory. However, a full assessment of the relative importance of sexual conflict versus cooperation must take account of the reproductive interests of the entire cast of nuclear genes and cytoplasmic genomes transmitted by the female. As a result of maternal inheritance, CGEs suffer the direct costs of male manipulation but receive no indirect benefits from the production of sexy sons. This nucleocytoplasmic difference in reproductive interests is likely to generate perpetual antagonistic coevolution between nuclear genes encoding male manipulation and CGEs that promote resistance by the female. The resulting evolutionary arms race parallels that generated by nucleocytoplasmic conflict over sex ratio.

This hypothesis predicts the involvement of cytoplasmic factors and/or nucleocytoplasmic interactions in genetic control of female resistance behaviour. Unfortunately, no studies have yet been designed to test this prediction. However, there is evidence for strong nucleocytoplasmic-interaction effects on female fitness [26]. Moreover, recent research has demonstrated a profound impact of mitochondrial haplotype on nervous-system development and cognitive ability [11]. In a study by Roubertoux *et al.*, total substitution of mtDNA was achieved by 20 repeated backcrosses between two strains of mice with different mtDNA haplotypes. Learning, exploration, sensory development and brain anatomy were all modified by interactions between mitochondrial and nuclear DNA. Assuming some level of the sex-specificity that characterizes many of the genetically-determined behaviours associated with copulation, remating and so on, these findings make the hypothesis that mitochondria could influence female behavioural responses to male manipulation plausible.

Maternal inheritance of mitochondria and the maladapted male

The sperm that never evolved

In sperm, the increased ATP demand that is associated with flagellar propulsion is met by mitochondria arranged in a tight helix around the flagellar basis of the midpiece [27]. Although motility is a crucial component of male fertility [28], the absence of paternal transmission precludes any direct evolutionary response to selection that acts on mitochondrial mutations that either reduce or enhance male fitness. In the case of a deleterious mutation, the equilibrium frequency of a mutant, mitochondrial haplotype ($\hat{q}$) is determined by a balance between its mutation rate in the female germ line (μ_f), and the intensity of selection acting on females (s_f) that have the mutation [29]. If selection is relatively weak,

$$\hat{q} \approx \frac{\mu_f}{s_f} \qquad \text{(Eqn 1)}$$

Because egg and sperm are under disruptive selection for size and motility [30], sexual asymmetry in selection might be most extreme for mitochondrial mutations that influence gamete function. In humans, mtDNA abnormalities, including nucleotide substitutions, deletions and insertions, result in poor sperm motility (asthenozoospermia), a common cause of male infertility [27,31]. Asthenozoospermia-associated mtDNA mutations frequently have no discernable negative fitness consequences for females [32]. As recognized by Frank and Hurst [29], such an asymmetrical selective filter can maintain mitochondrial mutations with highly deleterious, male-specific effects at an appreciable frequency (e.g. $\hat{q} \approx 0.01$ if $\mu_f = 10^{-4}$ and $s_f = 0.01$).

Similarly, maternal inheritance limits the spread of mitochondrial mutations that enhance sperm motility, competitive ability and fertilization success [24]. In a population that is subject to both selection and genetic drift, the fixation probability of a favourable mitochondrial mutation is $\sim 2s_f$ (twice the selection coefficient in females). Consider a hypothetical mtDNA mutation that affects the oxidative phosphorylation (OXPHOS) system, resulting in a slightly increased maximum rate of ATP production. In mammals, mature sperm contain <100 mitochondria [31]. To fertilize an egg, sperm must evade the female immune system (macrophages and antisperm antibodies), traverse cervical mucus, cross the utero-tubal junction, encounter an oocyte and finally penetrate the zona pellucida and egg plasma membrane. In the context of the polyandrous mating systems of most mammals [33], a mtDNA mutation conferring even a small increase in sperm velocity could considerably enhance the fertilization success of the male.

Strong evidence that mitochondrial haplotype determines sperm mobility and competitive ability has recently been reported for *Gallus domesticus* [34]. Forty-seven percent of sperm produced by males from lines that were artificially selected for low sperm mobility contained aberrant mitochondria compared with 4% aberrant sperm in males that were selected for high mobility. Sperm mobility is maternally-inherited and a female-based selection regime was used to select for high and low mobility. Sequencing the entire mitochondrial genome of males from the high and low mobility lines revealed only six nucleotide substitutions between the lines, and the authors hypothesize that a single A-to-G substitution in the gene encoding tRNA Arg might be responsible for the difference in mobility. These results are particularly interesting, because, in birds, males are the homogametic sex and sperm dysfunction cannot therefore be attributed to sex-chromosome hemizygosity.

By contrast, a mutation that boosts the ATP production rate could be neutral or even detrimental for females. The immotile oocyte has abundant mitochondria. The human egg, for example, contains $\sim 200\,000$ mtDNA copies, comprising nearly 50% of total cellular DNA [35]. Because OXPHOS is the major endogenous source of reactive oxygen species (ROS), an elevated metabolic rate would result in more oxidative damage to DNA and other essential cellular components [36]. Lacking protective histones [37], mitochondrial genomes are particularly sensitive to the toxic and mutagenic effects of ROS. Indeed, natural selection on mitochondria to minimize oxidative damage is likely to act in the opposite direction to sexual selection for enhanced sperm motility, and might therefore contribute to the evolutionary stability of maternal inheritance of mitochondria, despite its inhibitory effect on sperm evolution. An exception to strictly maternal mtDNA transmission occurs in bivalve mollusks. Doubly uniparental inheritance of mitochondria partially circumvents the asymmetrical selective filter and is associated with accelerated evolution of paternally transmitted mtDNA (Box 3).

Given the restricted capacity of mitochondria to evolve adaptively for sperm function, selection on the alternative options for increasing sperm mobility is likely to be intense (e.g. tail length and shape: traits encoded by nuclear genes that can respond to selection). The female-limited evolutionary response in mitochondria might therefore contribute to taxonomic diversity in sperm morphology. It could also explain why, in insects, homo-population males sometimes lose in sperm competition with hetero-population males [38]. Although it is not known how the mitochondrial derivatives of insect sperm contribute to motility [39], theoretically, population differences in the competitive ability of sperm could result from divergent selection on mitochondria in females rather than from population-specific selection in males.

The fragile male

Constraints on the ability of selection to hone mitochondria for functioning in males might have implications that extend beyond the effects on sperm performance [29]. Mutations in the mitochondrial genome are increasingly implicated in a wide range of pathologies, encompassing ageing, cancer and degenerative neurological diseases [40,41]. These diseases commonly involve tissues with increased metabolic requirements, such as those in heart, skeletal muscle and brain. Compared with females, males typically exhibit reduced lifespan and greater susceptibility to disease [42,43]. Undoubtedly various factors, such as male hemizygosity for the X-chromosome and the

Box 3. Doubly uniparental inheritance of mtDNA in bivalve mollusks

An intriguing exception to strict maternal mtDNA inheritance occurs in three bivalve lineages (marine mussels, freshwater mussels and marine clams). Females transmit 'F mtDNA' to both daughters and sons. Sons also inherit 'M mtDNA' from their fathers. The distribution of these two mitochondrial types in sexually-mature males is particularly interesting [55,56]. F mtDNA is predominant in somatic tissues, whereas M mtDNA is predominant in the testes. Sperm contain only M mtDNA. This pattern of doubly uniparental inheritance (DUI) partially circumvents the constraints that are associated with maternal mtDNA transmission, and should facilitate the adaptive evolution of paternally-inherited mtDNA for sperm performance. Consistent with this interpretation is the fact that M lineages evolve more rapidly than F lineages [57]. This pattern generally occurs in both synonymous and non-synonymous substitutions.

The sperm of these bivalves possess few mitochondria (e.g. five in *Mytilus*), and the precise mechanisms enabling paternal transmission are not well understood. However, in *M. edulis*, sperm-derived mitochondria aggregate into a single blastomere in male but not in female early-stage embryos and this is hypothesized to be a crucial step in the process through which paternal mitochondria come to predominate in the male germ line [56]. Nonetheless, breeding experiments and phylogenetic analyses indicate that, in marine mussels (Mytiloida), paternal-mtDNA transmission can break down. In such cases, maternal mitochondria enter the paternal transmission route, triggering *de novo* divergence between the F genome and the newly-recruited M genome. This phenomenon, termed masculinization or gender switching, has occurred at least five times in the evolution of Mytiloida [58]. By contrast, in freshwater mussels (Unionoida), there is no evidence of evolutionary loss of paternal-mtDNA transmission over the past 200 million years [59]. The stability of DUI in unionoids is associated with the presence of a 185-codon extension of the cytochrome c oxidase II (*MTCO2*) gene, although whether this is a cause or a consequence of increased DUI fidelity is unknown. Sequencing studies suggest the *MTCO2* extension is evolving in a non-neutral fashion and is likely to be the most rapidly evolving mitochondrial domain identified [60].

increased exposure of males to environmental stresses, contribute to these sexual differences. Nonetheless, at least in mammals, it appears that males have a greater basal metabolic rate than females [44]. Consequently, mitochondria that have evolved in response to selection in the female metabolic environment are likely to be prone to increased rates of ROS-related damage when functioning in males. This should lead to a greater rate of accumulation of deleterious mitochondrial mutations in male somatic tissues, and to a more rapid arrival at the mutational threshold level, beyond which OXPHOS activity becomes inadequate and mitochondrial disease is manifested [41]. The inability to transmit mitochondria might therefore be the Achilles' heel of the male sex.

The results from a study by Trifunovic and colleagues, in which mice were genetically engineered to express a 'mtDNA-mutator phenotype', provide evidence for a causal relationship between mitochondrial mutations and ageing [10]. Elevated rates of somatic mtDNA mutations were associated with a significantly reduced lifespan and a premature onset of ageing-related phenotypes, including osteoporosis, marked curvature of the spine and extensive hair loss. The association of somatic mtDNA mutations with extensive hair loss suggests a possible role for mitochondria in male-pattern baldness, an age-dependent trait that exhibits both maternal and paternal influences but whose precise genetic basis remains unclear [45]. Particularly striking was the impact of mtDNA mutations on male fertility. In matings between eight mtDNA-mutator males and 16 wild-type females, only one male successfully sired a litter, and this was abnormally small. By contrast, in crosses between wild-type males and mtDNA-mutator females, 93% of females became pregnant, giving birth to one or two litters of normal size.

Concluding remarks

Traditionally, the individual has been viewed as a unit of selection in which the selfish activity of individual genes is held in check by selection favouring integrated functioning of the genome as a whole [46]. Moreover, the importance of CGEs has been downplayed, as a consequence of the focus of the modern synthesis on nuclear genes and mendelian inheritance. Shifting from this perspective, Lewis Thomas, in his classic, popular-science account of the cell [47], mused that he might be taken for '… a very large, motile colony of respiring bacteria, operating a complex system of nuclei, microtubules, and neurons for the pleasure and sustenance of their families …'. Molecular genetic data and evolutionary theory have now converged to lend credence to Thomas' speculative self-portrait. Although many of the ideas in this article are hypothetical, controversial and require empirical investigation, it is nonetheless clear that, in the processes of eukaryote development, reproduction and evolution, mitochondria and other CGEs are emerging as more influential players than assumed previously.

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