

Research review

Inheritance and recombination of mitochondrial genomes in plants, fungi and animals

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Summary

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It is generally assumed that mitochondrial genomes are uniparentally transmitted, homoplasmic and nonrecombining. However, these assumptions draw largely from early studies on animal mitochondrial DNA (mtDNA). In this review, we show that plants, animals and fungi are all characterized by episodes of biparental inheritance, recombination among genetically distinct partners, and selfish elements within the mitochondrial genome, but that the extent of these phenomena may vary substantially across taxa. We argue that occasional biparental mitochondrial transmission may allow organisms to achieve the best of both worlds by facilitating mutational clearance but continuing to restrict the spread of selfish genetic elements. We also show that methodological biases and disproportionately allocated study effort are likely to have influenced current estimates of the extent of biparental inheritance, heteroplasmy and recombination in mitochondrial genomes from different taxa. Despite these complications, there do seem to be discernible similarities and differences in transmission dynamics and likelihood of recombination of mtDNA in plant, animal and fungal taxa that should provide an excellent opportunity for comparative investigation of the evolution of mitochondrial genome dynamics.

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Introduction

Early research on mitochondrial genomes focused primarily on animal mitochondrial DNA (mtDNA), and has led to the widely held assumptions that all mitochondrial genomes are uniparentally inherited, homoplasmic, and nonrecombining. These assumptions have had a strong influence on many areas of evolutionary inquiry, but have only recently been subject to systematic challenge (Birky, 1995; Ladoukakis & Zouros, 2001b;

Ballard & Whitlock, 2004). Here, we review the current body of knowledge on properties of mitochondrial genomes in plants and fungi, as well as animals, and show that these common assumptions are often violated. We then discuss the evolutionary implications of departure from uniparental, homoplasmic, and nonrecombinational transmission of mtDNA with regard to two important evolutionary phenomena associated with mtDNA: the accumulation of deleterious mutations and the spread of selfish elements. We posit that

occasional biparental reproduction and recombination probably occur at a high enough frequency to counter mutation accumulation, but likely not often enough to allow the spread of selfish mitochondrial elements.

Mitochondrial genomes are smaller than nuclear genomes, though they vary substantially in size across taxa from the relatively small animal mitochondrial genome (14–20 kb) to the larger and highly variable higher plant genome (200–2500 kb). Across eukaryotes, mitochondrial genomes contain an average of 40–50 genes which perform five basic processes (Burger *et al.*, 2003). These physical contrasts among mitochondrial genomes among phyla are well documented (Wolstenholme & Fauron, 1995; Burger *et al.*, 2003), but the dynamic properties of mitochondrial genomes are not as well understood. Profound differences in the mechanisms of inheritance of heteroplasmy and recombination and the frequency in mitochondrial genomes are likely to have important evolutionary implications.

Inheritance

The nuclear genome generally transmits copies of itself to the next generation via fair meiosis involving strict segregation. In contrast, cytoplasmic genome segregation is less equitable and more complex. Differential transmission of mitochondrial genes can occur both by differential replication of mitochondrial genomes in heteroplasmic cells and by differential segregation of mitochondrial genomes during mitosis and meiosis.

Differential genome replication

In contrast to nuclear genomes, multiple mitochondrial genomes populate each cell, can replicate more than once per cell cycle, and can be differentially transmitted to daughter cells (Birky, 1983; Andersson, 1999). This sets the stage for a situation in which certain mitochondrial genomes might replicate and be transmitted more often than others.

There are multiple ways in which differential replication of mitochondrial genomes can occur. Several studies have found a relationship between replication rate and distance from the nucleus, with mitochondrial genomes closer to the nucleus having higher replication rates (Mignotte *et al.*, 1987; Davis & Clayton, 1996). High rates of replication in the mutant 'petite' mitochondrial genomes in yeast relative to wild-type mitochondrial genomes have been ascribed to a high number of replication origins in mutant genomes (Williamson, 2002). A number of other mitochondrial mutations, characterized in animals and fungi, and ranging from point mutations to insertions and deletions, seem to confer relatively high replication rates on their genomes (Bertrand *et al.*, 1980; Griffiths, 1992; Chinnery *et al.*, 2000; Schwartz & Vissing, 2002). High replication rates in mutated genomes may be linked to selection for a threshold level of respiratory performance that favors accelerated production of mitochondria (and their

attendant genomes) that respire at below-normal levels (Griffiths, 1995).

Differential segregation in meiosis and mitosis in plants

Maternal transmission of mtDNA appears to be the predominant mode of mitochondrial inheritance in plants, and is likely to be enforced by two mechanisms. First, the sperm that ultimately fertilizes the egg undergoes a drastic reduction in mitochondrial numbers during development and carries few mitochondria relative to the egg (Miyamura *et al.*, 1987; Russell, 1987; Sodmergen *et al.*, 2002). Secondly, mechanisms that prevent the transmission of paternal cytoplasm to the zygote or cause the subsequent degradation of paternal mtDNA are numerous and common (Mogensen, 1996). Nevertheless, paternal transmission resulting in biparental inheritance of mitochondria has been documented in several plant taxa (Neale *et al.*, 1989; Erickson & Kemble, 1993; McCauley *et al.*, 2005). Compared to the substantial evidence for the existence of biparental transmission in plastids, however, evidence for biparental mitochondrial transmission is sparse (Mogensen, 1996; Havey, 1997; Vaillancourt *et al.*, 2004).

Differential segregation in meiosis and mitosis in fungi

The rules of organelle inheritance in fungi are more complex than in plants or animals. Modes of sexual reproduction and exclusion of paternal mitochondria are variable, and both biparental and uniparental inheritance are common (reviewed in Taylor, 1986).

In some of the Basidiomycetes, haploid mating types fuse and nuclei from both mating types are reciprocally exchanged and uniformly distributed in the heterokaryon. Mitochondria migrate across the zone of fusion in some taxa (Smith *et al.*, 1990) and not in others (May & Taylor, 1988). Even with high biparental mitochondrial contribution, however, progeny of the dividing zygote usually contain the mitochondrial genome of only one parent. Similarly, in laboratory yeast, fusion of parental types results in a more equitable contribution of mitochondria from both parents to the zygote than is typical for plants or animals (Birky, 1995), but heteroplasmy rarely persists through later zygotic divisions. Explanations for this phenomenon vary across fungal taxa, from the selective elimination of the mitochondria of one strain postfertilization (*Cryptococcus neoformans*; Yan & Xu, 2003) to the poor mixing of parental mitochondrial genomes and maintenance of separated positions in the zygote (*Saccharomyces cerevisiae*; Callen, 1974; Strausberg & Perlman, 1978; Nunnari *et al.*, 1997). Nevertheless, persistence of mtDNA contributed by both mating types has been documented on several occasions (Kawano *et al.*, 1987; Smith *et al.*, 1990; Sakurai *et al.*, 2004), even in anisogamous fungi (Yang & Griffiths, 1993).

The finding that biparental inheritance occurs in anisogamous taxa, along with the observation that many isogamous

taxa have uniparental inheritance (Nunnari *et al.*, 1997; Peters *et al.*, 2004), refutes the notion that anisogamy has evolved as a mechanism to prevent biparental transmission of cytoplasmic genomes. Interestingly, mitochondrial plasmids, defined as small extragenomic mtDNA molecules, are often transmitted biparentally in fungi and appear to facilitate the transmission and persistence of paternal mitochondrial genomes (Yang & Griffiths, 1993).

Differential segregation in meiosis and mitosis in animals

Similar to plants, paternal animal mtDNA does not generally persist through zygotic development. Loss of zygotic paternal mtDNA through selective degradation has been shown to occur in mice (Kaneda *et al.*, 1995), and is suspected in a wide range of taxa. Degradation of paternal DNA has even been documented in a case in which a relatively high proportion of paternal mitochondria enter the egg (Meusel & Moritz, 1993). Thus, it seems unlikely that paternal mtDNA regularly persists into later developmental stages (Houshmand *et al.*, 1997).

There are, however, a few documented cases of persistence of paternal mtDNA beyond early zygotic stages into adulthood (Kondo *et al.*, 1990; Gyllensten *et al.*, 1991; Birky, 2001; Schwartz & Vissing, 2002). In addition, indirect evidence for paternal leakage comes from the growing number of studies reporting heteroplasmy (Magoulas & Zouros, 1993; Kvist *et al.*, 2003) and recombination (Ladoukakis & Zouros, 2001b; Piganeau *et al.*, 2004). In these cases, paternal leakage is often cited as the explanation for the coexistence of genetically distinct mtDNA lineages. One unique case of paternal transmission of mitochondrial DNA is the doubly uniparental inheritance (DUI) that characterizes some bivalves (e.g. Ladoukakis & Zouros, 2001a; Passamonti *et al.*, 2003). In these species, females have only maternally transmitted mtDNA, but male progeny have maternally transmitted mtDNA in somatic tissues and paternally transmitted mtDNA in gonadal tissues.

Mitotic divisions can also result in differential mitochondrial segregation. In particular, the hypothesized sharp reduction in mitochondrial genome number ('bottleneck') that accompanies oogenesis has received a great deal of attention as a phenomenon that may be of particular relevance in understanding the evolutionary dynamics of mitochondrial genomes (Koehler *et al.*, 1991; Poulton *et al.*, 1998). Direct visual evidence for bottlenecking in mitochondrial number and subsequent amplification of the bottlenecked organelles during oogenesis is available. A recent review of electron micrographs of different germline cell stages found 10-fold reductions in mitochondrial number in germ cells relative to primary oocytes (Jansen, 2000). When mitochondrial numbers are dramatically reduced, random choice of molecules for replication and more systematic biases in which mitochondria are subsequently amplified in the oocytes can result in rapid changes in

the frequency of different mitochondrial haplotypes over generations. Consequently, bottlenecking of mitochondrial numbers can lead to high variation in mitochondrial genomic makeup within and between populations.

Selfish elements

Differential transmission of mitochondrial genomes can also be mediated by selfish genes, defined as genes that have a replication and transmission advantage at the expense of other genes.

The best known selfish mitochondrial genes are those that cause cytoplasmic male sterility (CMS) in angiosperms. CMS is a phenomenon in which pollen development is aborted in normally hermaphroditic plants, resulting in phenotypically female individuals. CMS is widespread in the angiosperms, very well studied, and significant in its impact on phenotypes and population dynamics (Frank, 1989). Research suggests that, in most cases of CMS, pollen abortion results in higher seed production by females (van Damme & van Delden, 1984; Manicacci *et al.*, 1998). As a result, individuals carrying CMS mitochondria increase in frequency at the expense of individuals carrying wild-type mitochondria, and at the expense of nuclear genes, which are transmitted both through pollen and through seeds. One interesting aspect of CMS in the current context is that the mtDNA transmission advantage is determined by the phenotype of the whole plant, instead of being strictly a result of heteroplasmy and competition within cells. Unlike most examples of selfish mitochondrial mutants, therefore, uniparental inheritance, with the resulting paucity of competition among divergent mitochondrial genomes within cells, is not an obstacle for selfish transmission.

In fungi, the most well-known selfish mitochondrial genes are the petite mutants of yeast (Williamson, 2002). Petite mitochondrial genomes are characterized by large deletions and an inability to respire. Because yeast can metabolize via fermentation (i.e. are facultative aerobes), the petite mutants are not unconditionally lethal, but do result in lowered cell fitness relative to the wild type in standard media. Petite mutant genomes often contain more replication origins than wild-type genomes (MacAlpine *et al.*, 2001), which can result in a nearly 2-fold transmission advantage whenever the two coexist within a cell.

A number of selfish mitochondrial genomes and selfish mitochondrial plasmids are known from several taxa of obligate aerobic fungi. These selfish mitochondrial elements arise from rearrangements, deletions, and insertions in mtDNA, and are implicated in phenotypes such as increased cell senescence, decreased cell senescence, and retarded hyphal growth (Bertrand *et al.*, 1980; Griffiths, 1992; Nakagawa *et al.*, 1998). Despite this wide range of genomic and phenotypic effects, all of these selfish mitochondrial genomes and mitochondrial plasmids over-replicate at the expense of wild-type mitochondrial genomes and plasmids. In some cases, the over-replication of

dysfunctional mitochondrial genomes results in cell death (Griffiths, 1992). In others, however, the competitive maintenance of wild-type mitochondrial genomes at low levels allows the retention of cell viability (Bertrand *et al.*, 1980; Griffiths, 1995). This phenomenon is similar to the among-cell competitive maintenance of wild-type cells demonstrated experimentally in yeast petite mutants by Taylor *et al.* (2002). While mitochondrial genomes and mitochondrial plasmids have transmission rules that can be independent of each other, they also interact extensively. Plasmids insert into and bud off from the mitochondrial genome. These interactions can affect both the transmission properties and the degree of selfishness of the mitochondrial plasmids (Yang & Griffiths, 1993; Nakagawa *et al.*, 1998).

Evidence hinting at the existence of other selfish elements in fungi has come to light in recent years. In heterothallic fungi, haploid strains (monokaryons) generally share nuclei reciprocally and homogeneously following fusion in the heterokaryon, but maintain separate mitochondria. However, there are cases in which nuclei are not reciprocally exchanged. In this instance, one monokaryon donates nuclei ('male') while the other receives nuclei ('female'). While direct evidence is not yet available, Aanen *et al.* (2004) suggest that nonreciprocal exchange of nuclei can best be explained by the presence of selfish mitochondria that can suppress the nuclear-donating capacity of their monokaryon and thereby ensure that their mitochondrial genome is represented in the fruiting dikaryon. This possible 'male'-suppressing phenomenon in fungi is similar to plant CMS in the conflict that arises between nuclear and mitochondrial genomes, but also because the mitochondrial genome produces a somatic phenotype that enhances mitochondrial transmission relative to mitochondria from other strains, and does so without heteroplasmy and competition within cells.

Although selfish (male-killing or feminizing) cytoplasmically transmitted parasitic bacteria are common in insects, documented examples of mitochondrial selfish elements in

animals are rare (Hurst *et al.*, 1996). There are a few known cases of mitochondrial genomes that replicate at higher rates because of their smaller size compared to wild-type genomes (Rand & Harrison, 1989; Wallace, 1992). In general, however, selfish mitochondria in animals are reported much less often than in plants or fungi. The scarcity of selfish animal mtDNA may be related to the stability and small size of animal mitochondrial genomes relative to their counterparts in plants and fungi (Budar *et al.*, 2003).

Heteroplasmy

Biparental inheritance is an important source of heteroplasmy, which is the coexistence within an individual of genetically distinct mitochondrial genomes. Heteroplasmy can occur via the coexistence of mitochondrial genomes of either different nucleotide lengths (length heteroplasmy) or different nucleotide compositions (site heteroplasmy). Length heteroplasmy can involve large-scale insertions and deletions (Boursot *et al.*, 1987; Volz-Lingenhohl *et al.*, 1992; Gillham, 1994), but more often seems to derive from errors in mtDNA replication resulting in variation in tandem repeat number in or near the control region (e.g. Berg *et al.*, 1995; Lunt *et al.*, 1998; Townsend & Rand, 2004). Site heteroplasmy is reported less frequently than length heteroplasmy (Table 1), but is of special interest to evolutionary biologists because the coexistence of mitochondrial genomes that differ in the placement of deleterious point mutations is required for recombinational repair of mutational degradation and generation of novel recombinant genotypes (Lynch & Blanchard, 1998).

Plants

In plants, reports of heteroplasmy caused by paternal leakage are rare (Mogensen, 1996; Hattori *et al.*, 2002). Interestingly, plants seem to contrast sharply with animals in the frequency of heteroplasmy in natural populations because of variation in

Table 1 The distribution of reported heteroplasmy in animals, plants and fungi

	Heteroplasmy type			Total	Hybridization ¹	Phylogeography	Paternal leakage	Studies using PCR	Without PCR	Before 1989 ³
	Length	Site	Unknown							
Animals	56	18	6	80	11 (8 in lab)	30	15 (6 DUI) ²	50	21	15
Plants	2	5	2	9	5 (4 in lab)	1	6	5	3	2
Fungi	2	1	10	13	9 (9 in lab)	1	11	1	12	5

¹Number 'in lab' indicates heteroplasmy detected in laboratory-generated hybrids.

²'DUI' indicates heteroplasmy via doubly uniparental inheritance.

³Polymerase chain reaction (PCR) became widespread after 1988.

'Heteroplasmy type' refers to whether the heteroplasmy is caused by changes in genome length ('Length'), point mutations ('Site'), or unknown ('Unknown'). 'Hybridization' shows the number of reports of heteroplasmy in each organismal type linked to hybridization. 'Phylogeography' represents the number of reports of heteroplasmy from phylogeographic studies for each organismal type. Finally, we present the number of reports of heteroplasmy in studies using PCR ('Studies using PCR'), studies without PCR ('Studies without PCR'), and in studies taking place before PCR was widespread ('Before 1989'). Multiple reports of heteroplasmy within a single genus are lumped into one report or genus.

tandem repeat number. Although tandem repeats are fairly common in plant mtDNA (Sperisen *et al.*, 2001), our literature survey of heteroplasmy in plants failed to uncover a single example of intra-individual variation in tandem repeat number. This is most likely a consequence of the infrequent use of plant mtDNA for phylogeographic research (Städler & Delph, 2002) where the majority of animal tandem repeat heteroplasmy has been found (see the section 'Study biases' below).

Some discussion of mitochondrial heteroplasmy in plants is associated with cytoplasmic male sterility (Maletskii, 1995; Andersson, 1999), which may be a result of the fact that sexual phenotypes of male-sterile and male-fertile mitochondria are easily observed (see the section 'Study Biases' below). Heteroplasmy has also been observed in a line of mutant maize *Zea mays* heteroplasmic for a mitochondrial deletion (Gu *et al.*, 1993; Yamato & Newton, 1999). However, most of the studies examining and reporting heteroplasmy in plants involve hybridization between different strains or species (Table 1). Given the apparent slow rate of point mutation in plant mtDNA (Wolfe *et al.*, 1987, but see Cho *et al.*, 2004), this bias may be attributable to the assumption that heteroplasmy is unlikely to be observed within a single species.

Another source of heteroplasmy that is known only from higher plants is the presence of mitochondrial genes on subgenomic molecules occurring at very low ('substoichiometric') levels in cells. Plant mitochondrial genomes are distinguished from those of animals and fungi by undergoing frequent inter- and intramolecular recombination in areas of repeated sequences (Abdelnoor *et al.*, 2003). This recombination can produce small subgenomic molecules that contain only a portion of the genome. Plants can maintain these subgenomic molecules at very low frequencies over many generations, with the phenotypic effects of their genes left unexpressed (Small *et al.*, 1989). Interestingly, plants can then increase the copy numbers of these subgenomic molecules to normal levels over the course of a single generation, accompanied by the phenotypic expression of these genes.

Substoichiometric shifting in mtDNA has been found in wild *Phaseolus* species with an ancient, conserved cytoplasmic male sterility gene located on subgenomic molecules (Arrieta-Montiel *et al.*, 2001). In this system, the appearance of females across taxa is associated with the amplification of substoichiometric molecules containing the CMS gene. Amplification of a substoichiometric molecule and subsequent recombination have also been proposed to explain a novel duplication in maize *Z. mays* that is absent from its ancestor (Small *et al.*, 1989). These molecules may present an important mechanism for the widespread maintenance of heteroplasmy in plants and a source of novel genotypes through nonhomologous recombination. However, given the difficulty of detecting substoichiometric molecules with standard molecular techniques, the prevalence of substoichiometric molecules in nature is unknown.

Fungi

Heteroplasmy into later developmental stages seems to be rare in most fungi (Hintz *et al.*, 1988), despite the fact that the protoplasm fusion that accompanies sexual reproduction results in heteroplasmic zygotes (Economou *et al.*, 1987; Matsumoto & Futumasa-Nakai, 1996). In most cases, selection and segregation in mitotic divisions following fusion mean that heteroplasmy is quickly lost (Smith *et al.*, 1990). As mentioned above, however, biparental inheritance of mitochondria and persistent heteroplasmy have been documented (Kawano *et al.*, 1987; Yang & Griffiths, 1993). In addition, heteroplasmy of wild type and a number of different mitochondrial mutants has been found in strains of *Neurospora* and *Podospora* (Bertrand *et al.*, 1980; Bertrand *et al.*, 1985; Griffiths, 1992). In these cases, the mutant mitochondria lack essential genes, so cells either die as the mutant mitochondria eventually replace wild-type mitochondria or survive as a result of the maintenance of a low frequency of wild-type mitochondria (see the section 'Selfish elements' above). Interestingly, even cells that die because of a high frequency of mutant mitochondria can maintain heteroplasmy in progeny lines by transmitting the mutant mtDNA maternally before death (Griffiths, 1992).

Animals

Length heteroplasmy is common in animals (Table 1; reviewed in Lunt *et al.*, 1998), especially relative to plants and fungi, and site heteroplasmy seems to be rare (e.g. Lansman *et al.*, 1983; Meusel & Moritz, 1993; Taylor *et al.*, 2003; but see Zhao *et al.*, 2004). The apparent scarcity of site heteroplasmy may be linked to the quick return to homoplasmy during the bottlenecks that accompany transmission of mitochondria from parent to offspring (e.g. Poulton *et al.*, 1998; Rand, 2001). In addition, there are substantial logistical challenges to detecting heteroplasmy when the variant genomes differ by no more than a few base pairs (Bermingham *et al.*, 1986; Bendall *et al.*, 1996; Ladoukakis & Eyre-Walker, 2004).

The role of hybridization

Many of the documented examples of persistent heteroplasmy linked to paternal leakage in plants, animals and fungi involve hybrids (e.g. Borkhardt & Olson, 1983; Kondo *et al.*, 1990; Yang & Griffiths, 1993; Kaneda *et al.*, 1995; Laser *et al.*, 1997; Hattori *et al.*, 2002; Kitagawa *et al.*, 2002; Schwartz & Vissing, 2002). The link among hybridization, paternal leakage and heteroplasmy is not well understood. One possibility is that the tagging of paternal mtDNA for subsequent degradation, such as the ubiquitin labeling of mammalian sperm, does not function properly in hybrid individuals. An example of failure of ubiquitin labeling in a hybrid was

recently reported from a cross between cow eggs and wild guar sperm (Sutovsky *et al.*, 1999). Another possible explanation, at least in plants, for the relatively frequent detection of paternal mtDNA and heteroplasmy in hybrid progeny is that heteroplasmy stems not from paternal leakage but from hybridization-induced amplification of paternal-like mtDNA carried by the maternal parent in substoichiometric quantities (Laser *et al.*, 1997). Amplification of substoichiometric molecules is dependent on nuclear background in maize *Z. mays* (Laughnan *et al.*, 1981), and has been observed in protoplast fusion experiments in other species (Morgens *et al.*, 1984; Morgan & Maliga, 1987; Ozias-Akins *et al.*, 1988).

A causal association between hybridization and heteroplasmy could have important evolutionary implications. Specifically, there is a variety of empirical evidence suggesting that the lineage sorting and drift that occur during uniparental mitochondrial transmission will quickly eliminate heteroplasmy (e.g. Birky, 1983; Koehler *et al.*, 1991; Parsons *et al.*, 1997). This implies that heteroplasmy generated within a species might be transient. Thus, hybridization (or doubly uniparental reproduction) might be an important means by which genetically divergent mitochondrial genomes can meet and recombine. If this is the case, then hybrid zones may be important locations for the generation of novel mitochondrial haplotypes and mutational clearance.

Recombination

Even rare recombination can alleviate mutation accumulation (Charlesworth *et al.*, 1993), facilitate adaptive evolution (reviewed in Hurst & Peck, 1996), and complicate the determination of phylogeny (reviewed in Ballard & Whitlock, 2004). Accordingly, a wide range of eukaryotic taxa, including many plant and animal species and several species of fungi, have been surveyed for the presence of recombinant mtDNA. Most researchers now agree that plant mitochondrial genomes undergo occasional recombination (Lonsdale *et al.*, 1988; Gillham, 1994; Birky, 2001; Städler & Delph, 2002; Bergthorsson *et al.*, 2003). There is even more evidence for recombination in fungi (Taylor, 1986; Gillham, 1994; Saville *et al.*, 1998; Birky, 2001). In particular, a large body of data provides confirmation that mitochondrial recombination occurs readily in yeast (e.g. Dujon *et al.*, 1974; Birky *et al.*, 1982; Taylor, 1986; MacAlpine *et al.*, 1998). Fungi also contain mitochondrial plasmids that can be transmitted paternally (and even horizontally through somatic hyphae) and can move in and out of mitochondrial genomes. This phenomenon may increase the probability of gene transfer between genetically distinct mitochondrial genomes (Yang & Griffiths, 1993).

Although animal mtDNA possesses the necessary machinery for recombination (Pont-Kingdon *et al.*, 1995; Thyagarajan *et al.*, 1996; Tang *et al.*, 2000; Kajander *et al.*, 2001), there is

little direct support for mitochondrial recombination (Birky, 2001; Elson *et al.*, 2001; Innan & Nordborg, 2002; Ballard & Whitlock, 2004; Berlin *et al.*, 2004; Piganeau & Eyre-Walker, 2004). The few convincing examples of recombination generally involve either bivalves with DUI (Zouros *et al.*, 1992; Ladoukakis & Zouros, 2001a; Passamonti *et al.*, 2003) or interspecific or interstrain hybrids (reviewed in Ballard & Whitlock, 2004). There is one recent report of recombination in humans (Kraytsberg *et al.*, 2004) that has been interpreted as definitive (Ladoukakis & Eyre-Walker, 2004). There is also a growing body of indirect evidence pointing to the likelihood of recombination in animal mtDNA (Ladoukakis & Zouros, 2001b; Piganeau *et al.*, 2004; Gantenbein *et al.*, 2005), but this type of evidence has been treated with some skepticism (Elson *et al.*, 2001; Eyre-Walker & Awadalla, 2001; Piganeau & Eyre-Walker, 2004).

Study biases

Patterns in the recorded incidences of heteroplasmy and recombination may be influenced by study biases (Table 1). One obvious example is the apparent link among hybridization, paternal leakage and persistent heteroplasmy. Given the established difficulty of detecting heteroplasmy (Gyllensten *et al.*, 1985; Milligan, 1992; Rokas *et al.*, 2003) and recombination (Posada & Crandall, 2001; Rokas *et al.*, 2003) when there is little divergence between mitochondrial genomes, the connection between hybridization and heteroplasmy could simply be a result of ease of detection (Ladoukakis & Zouros, 2001a; Passamonti *et al.*, 2003; Rokas *et al.*, 2003). If this were the case, intraspecific paternal mitochondria genome transfer may be more common than is generally supposed. Polymerase chain reaction (PCR)-based methods, which are now widely used, may reduce this detection bias.

A good example of the increased effectiveness of PCR in detecting paternal transmission is provided by Gyllensten *et al.* (1991). In this study, the authors used PCR to detect paternal mitochondrial DNA present at extremely low frequency in hybrid mice. The authors had used lower-resolution techniques in an earlier study (Gyllensten *et al.*, 1985) of the same cross, but failed to detect paternal mitochondrial DNA. The success of this later study demonstrates that earlier interpretations that paternal transmission (or low-frequency heteroplasmy) is extremely rare may have been incorrect.

It should be noted that PCR will be helpful in detecting heteroplasmic genomes at low frequency, particularly in those cases in which paternal leakage is frequent but results in only few mitochondria transmitted to progeny. In situations in which paternal leakage occurs more rarely (even if the numbers of mitochondria leaked are high), a larger sample of zygotes will be necessary to detect heteroplasmy (Birky, 2001). Similarly, plant mtDNA heteroplasmy produced by substoichiometric subgenomic molecules may very well be underreported because most standard molecular techniques

do not detect mitochondrial haplotypes present at extremely low copy number.

Mitochondrial variants may also lack obvious phenotypic expression, which can hamper detection of mitochondrial biparental inheritance and heteroplasmy. This may in part explain why heteroplasmy underlying very visible phenotypes of chloroplast mutants has been well documented (Mogensen, 1996). Similarly, the observation of heteroplasmy in plants with cytoplasmic male sterility (Maletskii, 1995; Andersson, 1999) may be attributable to its unique and obvious phenotypic expression.

Another potential source of bias is study effort. For example, studies of mitochondrial inheritance in plants have largely focused on crop and outcrossing species that may exhibit reduced biparental inheritance (Reboud & Zeyl, 1994). Similarly, the fact that the most common reports of nonhybrid-associated heteroplasmy are from animals may also reflect disproportionate study effort. Animal mtDNA may be the focus of more study than plant or fungal mtDNA because of the well-established links between mitochondrial mutations and heteroplasmy, and human diseases and aging (Linnane *et al.*, 1989). MtDNA is also very commonly used for phylogeographic studies within animal species (reviewed in Avise, 2000; Table 1). In contrast, mtDNA is very rarely utilized in intraspecific phylogeographical research in plants (Avise, 2000; Städler & Delph, 2002), and plant and fungal phylogeography has received much less attention than phylogeography in animals (Avise, 1998; Bermingham & Moritz, 1998). These marked differences in the degree of use of plant and fungal mtDNA for medical studies and for intraspecific phylogeography may explain both the apparent paucity of tandem repeat heteroplasmy in plants and fungi relative to animals and the disproportionate number of reports of heteroplasmy in plants and fungi linked to model species and species of commercial importance.

Interestingly, detection of mitochondrial recombination does not seem to be as obviously affected by biases in study effort as is heteroplasmy. Despite the thousands of phylogeographical studies conducted using animal mitochondrial DNA, there remain only a few convincing direct reports of evidence for recombination. However, though controversy remains, recent surveys of recombination in mtDNA increasingly point to the likelihood of mtDNA recombination in a wide variety of animal taxa (Ladoukakis & Zouros, 2001b; Piganeau *et al.*, 2004).

There is a general consensus that plant and fungal mitochondrial DNA do engage in occasional recombination. Data pointing to recombination in these phyla have largely come from cytological and molecular studies of model organisms, in contrast to the heavy focus on phylogeography of natural populations in animals. Perhaps the more frequent application of techniques more commonly used for plant and fungal mtDNA to animal mtDNA would reveal more definitive evidence for or against recombination.

Implications of departure from homoplasmy, strict maternal inheritance, and no recombination for mutation accumulation and repression of selfish elements

Theory suggests that uniparental cytoplasmic inheritance may be selectively favored by the host genome because it counters the spread of selfish biparentally inherited organelles or parasites (Grun, 1976; Cosmides & Tooby, 1981; Hoekstra, 1990; Law & Hutson, 1992; Hurst, 1996; but see Birky, 1995 and Whittle & Johnston, 2002). However, uniparental inheritance also drastically reduces the opportunities for heteroplasmy and recombination, leaving mitochondrial genomes vulnerable to the accumulation of deleterious mutations (Gabriel *et al.*, 1993; Lynch, 1996).

Our review suggests that violations of uniparental inheritance occur across plant, fungal and animal taxa, and may influence many evolutionary processes involving mtDNA. Here, we consider the evolutionary implications of occasional biparental transmission, heteroplasmy, and recombination with regard to the accumulation of deleterious mutations and the spread of selfish elements. We suggest that low, but nonzero amounts of biparental mitochondrial transmission may allow organisms to achieve the best of both worlds in terms of facilitating genetically relevant recombination and mutational clearance, but still maintaining selfish element control (also see Rispe & Moran, 2000).

Mitochondrial recombination and mutation accumulation

Theory suggests and empirical evidence demonstrates that occasional genetic recombination is required to clear deleterious mutations from a lineage (Charlesworth *et al.*, 1993; Poon & Chao, 2004). The connection between recombination and maintenance of genome integrity has led to the prediction that allegedly asexual mitochondrial genomes should be plagued with mutation accumulation (Lynch, 1996, 1997).

This prediction has found some support in a series of papers indicating that nonsynonymous mutations in the mitochondrial genome accumulate at an accelerated rate relative to the nuclear genome across animals, plants and fungi (Lynch, 1996, 1997; Lynch & Blanchard, 1998). However, mitochondrial genomes remain functional and integral to fitness (Burton *et al.*, 1999; Rand, 2001; Christie *et al.*, 2004). In addition, there is evidence for relaxed selection on male-expressed relative to female-expressed mitochondrial genes. These data suggest that the fitness of female-expressed mitochondrial traits is maintained effectively through selection (Frank & Hurst, 1996; Ruiz-Pesini *et al.*, 2000). A relevant question, also raised by other researchers (e.g. Birky, 1995; Bergstrom & Pritchard, 1998; Rand, 2001), is how mitochondrial genomes stay healthy, especially if recombination seems to be absent.

Perhaps the most likely scenario is that mtDNA does undergo recombination, but in a manner or on a scale that often escapes detection. Given the well-established difficulty of detecting rare recombination between similar sequences (Maynard Smith, 1999; Posada & Crandall, 2001; Wiuf, 2001), recombination may happen much more frequently than currently assumed.

This might be particularly likely given that the low rate of recombination required to counter mutation accumulation (Charlesworth *et al.*, 1993) may fall well below the current threshold of detection of methodologies for identifying mitochondrial recombination (M. Neiman and D. R. Taylor, unpublished). Moreover, there are additional mechanisms apart from mtDNA recombination that may provide an effective means of mutational clearance (Bergstrom & Pritchard, 1998; Martin & Herrmann, 1998; Rispé & Moran, 2000; Willett & Burton, 2003). Even if mutations are accumulating in mitochondrial genomes, the rate of accumulation is slow enough that severe fitness losses will occur on a time scale of tens of millions of years (Lynch & Blanchard, 1998). Mutation accumulation may thus not be a serious immediate problem for the integrity and function of mitochondrial genomes (Lynch & Blanchard, 1998).

Suppression of selfish elements

Uniparental inheritance is commonly thought to evolve as a nuclear trait countering the negative effects of selfish organellar genomes or cytoplasmic parasites (Grun, 1976; Cosmides & Tooby, 1981; Hoekstra, 1990; Hastings, 1992; Law & Hutson, 1992; Hurst, 1996) by reducing the within-host variance and opportunities for competitive advantage of selfish elements (Frank, 1996; Rispé & Moran, 2000). This raises the question of whether low levels of biparental inheritance may also substantially reduce the selfish element control that uniparental inheritance provides. We argue that it does not. If we assume that selfish mitochondrial mutants realize a transmission advantage by a competitive advantage within heteroplasmic cells, then the magnitude of biased transmission becomes vanishingly small as heteroplasmy becomes increasingly rare. Moreover, the transmission advantage realized during an episode of biparental transmission would need to more than offset cell-level selection against the element until the next episode of biparental transmission. In contrast, the same rare biparental transmission may generate opportunities for recombination with enough frequency to oppose mutational processes such as Muller's ratchet.

In essence, the two processes operate on two different orders of magnitude; selfish elements require a high enough frequency of biparental transmission and heteroplasmy to gain a transmission advantage before being lost by drift, whereas mutational clearance can occur with very little recombination (Charlesworth *et al.*, 1993). Thus, we suggest that the small amounts of biparental inheritance of mitochondria and

subsequent heteroplasmy that appear to be present in plants, fungi and animals are almost certainly too low to reduce the effectiveness of uniparental inheritance in selfish element control (also see Randerson & Hurst, 1999), and may even be a symptom of the minimal threat that selfish elements pose.

Whether occasional biparental inheritance is a mechanical accident or an adaptation to facilitate mutational clearance remains unknown. On the one hand, it seems likely that violations of strict uniparental inheritance are inevitable, analogous to the assumed impossibility of perfect DNA repair and replication. In this case, mutational clearance may be a lucky, unselected byproduct of imperfect enforcement. On the other hand, if leakage leads to recombination that is beneficial to genomes, it, like recombination *per se*, may be subject to selection.

Conclusions

Plants, animals and fungi are all characterized by the presence of different mechanisms at the genome replication, meiotic, and mitotic stages to prevent the transmission of paternal mtDNA. However, despite these mechanisms, paternal transmission has been repeatedly recorded across all of these taxa.

While animals, plants and fungi may differ in the extent to which heteroplasmy occurs, and in the mechanisms whereby it is both achieved and resolved, this review indicates that there are some important similarities. In general, we find that site heteroplasmy is rarely detected except when it is linked to hybridization, and hybridization may prove to be an important facilitator of heteroplasmy and recombination. In addition, we find that many instances of site heteroplasmy are attributable to paternal leakage. Length heteroplasmy seems to be common in animals but rare in plants and fungi. Plants are distinguished from the other taxa in that they may maintain heteroplasmy over many generations through the presence of substoichiometric subgenomic molecules, and experience the rapid phenotypic expression of heteroplasmic genomes through expansion of substoichiometric molecules to normal levels. It is not at all clear why plant mitochondrial genomes have this property and no cogent evolutionary explanation has been forthcoming in the literature. We also find that unintentional biases in the use of methodologies and study systems may contribute to significant underdetection of paternal leakage, heteroplasmy, and recombination, as well as misrepresentation of the distribution of these phenomena across taxa.

We bring these findings together to suggest that low but nonzero levels of biparental transmission, heteroplasmy and recombination may facilitate mutational clearance in mtDNA, but are likely to be rare enough that the control of the spread of selfish elements is not severely compromised.

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