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Review

Uniparental inheritance of mitochondrial and chloroplast genes: Mechanisms and evolution

(organelles/non-Mendelian inheritance/maternal inheritance)

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ABSTRACT **In nearly all eukaryotes, at least some individuals inherit mitochondrial and chloroplast genes from only one parent. There is no single mechanism of uniparental inheritance: organelle gene inheritance is blocked by a variety of mechanisms and at different stages of reproduction in different species. Frequent changes in the pattern of organelle gene inheritance during evolution suggest that it is subject to varying selective pressures. Organelle genes often fail to recombine even when inherited biparentally; consequently, their inheritance is asexual. Sexual reproduction is apparently less important for genes in organelles than for nuclear genes, probably because there are fewer of them. As a result organelle sex can be lost because of selection for special reproductive features such as oogamy or because uniparental inheritance reduces the spread of cytoplasmic parasites and selfish organelle DNA.**

Genes in chloroplasts were first detected by Baur (1) and Correns (2) in 1909 because their inheritance departed from the Mendelian rules. Much later, mitochondrial genes were identified in the same way. The non-Mendelian inheritance of organelle genes became manifest in two ways: the rapid segregation of alleles during vegetative (mitotic) reproduction and inheritance from one parent only. Vegetative segregation of chloroplast genes is a consequence of randomness of replication and partitioning of organelles and organelle DNA molecules at cell division (3). Uniparental inheritance proved to be even more complex; the variety of molecular and cellular mechanisms found in different organisms is matched only by the variety of hypotheses devised to explain the evolution of the phenomenon.

Genetics

There Are Many Different Patterns of Uniparental Inheritance. Correns found that chloroplasts are inherited only from the female parent in the four-o'clock (*Mirabilis jalapa*). Strictly maternal inheritance is shown diagrammatically in Fig. 1 *Left* with the example of maize, for which more progeny have been analyzed (compiled in ref. 4). Crosses of green females by mutant males (variegated plants with mutant white germ-line cells supported by sectors of green tissue) produce only green progeny; the reciprocal cross produces only mutant embryos. Baur found a different pattern in the geranium (*Pelargonium zonale*; Fig. 1 *Center*): some offspring inherited chloroplast genes from the female parent only; others, from both parents; and still others, from the male parent only. The reciprocal cross also gives a mixture of the three different kinds of progeny but in different proportions. The plants that inherit chloroplasts from both parents are variegated with green and white clonal sectors. Although the fertilized eggs (zygotes) are heteroplasmic, containing plastids of both genotypes, these segregate rapidly during vegetative cell divisions. Consequently, the mature plant consists of clonal sectors of homoplasmic mutant and wild-type cells.

The *Mirabilis* and *Pelargonium* inheritance patterns are often called maternal and biparental, respectively, but this terminology is not generally applicable. Looking at individual progeny, one sees that *Pelargonium* crosses produce a mixture of maternal, biparental, and paternal zygotes. Additional terminological problems appear in microorganisms that do not have differentiated male and female sexes (i.e., are isogamous). Fig. 1 *Right* diagrams the inheritance of mitochondrial genes in yeast (3). Haploid cells of mating types **a** and α carry different alleles of a mitochondrial gene (e.g., conferring resistance and sensitivity to an antibiotic). Haploid cells fuse to form zygotes that are heterozygous **a**/α and heteroplasmic ant^r/ant^s. During subsequent mitotic divisions, the mitochondrial alleles segregate so that virtually all daughter cells are homoplasmic after about 10 cell divisions. In addition, some clones produced by individual zygotes contain only ant^r or only ant^s cells. This is also a consequence of relaxed replication and partitioning of mtDNA: in some zygotes, only mitochondrial genomes from one parent are replicated and partitioned into buds, while those from the other parent remain in mother cells that die before the colony is examined. This inheritance pattern is similar to that of *Pelargonium* if one looks at single markers in zygote clones, except that the homoplasmic cells in a clone are individuals rather than differentiated cells within an individual.

Another way of looking at the variation in patterns of uniparental vs. biparental inheritance is to plot frequency distributions of the frequencies of alleles from the two parents in the progeny of different zygotes. Many different frequency distributions have been observed in different species and often in different crosses of the same species (e.g., refs. 5 and 6). The different patterns can be classified according to whether they contain uniparental or biparental zygotes, or both, as in Fig. 2. Pattern I (Um) is the same as Fig. 1 *Left*. Pattern II (UmB) is seen in *Oenothera* crosses in which most progeny inherit chloroplast genes from the female parent only, while a few inherit them from both parents. Pattern III (UBU) can be subdivided according to the relative numbers of genomes contributed by the two parents. Different crosses involving chloroplast genes in *Pelargonium* or mitochondrial genes in yeast show patterns IIIa–IIIc, depending on the nuclear and organelle genotypes of the parents. IIId (UU) is seen in the blue mussel (*Mytilus edulis*), in which there are two separate uniparental lineages, one transmitted via females and the other via males (7, 8). Patterns IV (BUp) and V (Up) are seen in gymnosperms.

In many cases sample sizes are insufficient to distinguish between patterns (e.g., between I and II or III). Moreover, the stochastic processes that can cause uniparental inheritance are probably always operating. Consequently, strictly uniparental inheritance is probably not as common as is generally believed. The inheritance of mtDNA in interspecific crosses of mice was believed to be strictly uniparental (9) until a more sensitive technique (PCR amplification) was used to detect low levels of paternal mtDNA (10). These pat-

Abbreviations: UPI, uniparental inheritance; BPI, biparental inheritance; mtDNA, mitochondrial DNA.

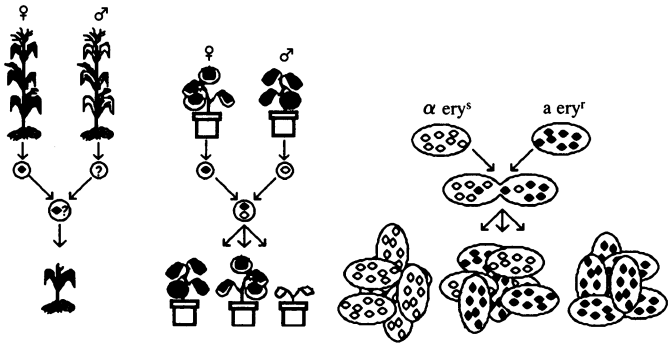

FIG. 1. Examples of uniparental inheritance in maize (*Left*), *Pelargonium* (*Middle*), and *Saccharomyces cerevisiae* (*Right*).

terns are for single markers; if recombination occurs, some zygotes classified as uniparental for an allele from one parent may contain alleles of another locus from the other parent. Recombination is frequent in the chloroplasts of *Chlamydomonas* (11) and the mitochondria of the fungi *Saccharomyces* (12, 13), *Schizosaccharomyces* (14), and *Aspergillus* (15). Recombinant restriction fragment-length polymorphism (RFLP) patterns have been found in some matings of the slime mold *Physarum*, but it is not clear whether these are due to recombination between the two parental mitochondrial genomes, intragenomic rearrangements, or plasmid integration (16). In contrast, there are a number of cases in which significant numbers of biparental zygotes are produced, but the organelle genomes from the two parents do not recombine. In plants, screens of progeny from sexual crosses detected no progeny that were recombinant for chloroplast genes (refs. 17 and 18). Two recombinant plastid genomes were recovered by stringent selection in plants reared from a very large number of fused somatic cells (19, 20), showing that chloroplast genes can recombine; the extreme scarcity of detectable recombination in crosses is probably due to a very low frequency of chloroplast fusion. No recombinants of the male and female mitochondrial lineages in blue mussel have been found, even though both genomes have been present in the fertilized egg and germ line cells of embryos in every generation (7, 8) for over five million years (21, 22). The absence of recombination in many organisms means that the inheritance of organelle genes is effectively asexual in those cases, even when it is biparental.

The division of patterns of inheritance into these classes is somewhat artificial because different species, or even different crosses in some species, produce from 0% to 100% uniparental zygotes. Consequently it would be more appropriate for many purposes to treat uniparental inheritance as a quantitative trait. If this is to be done, geneticists will have to estimate the frequency of markers from each parent in each biparental zygote whenever possible and publish the observed frequency distribution(s).

There Are Many Different Mechanisms of Uniparental Inheritance. The underlying mechanisms of uniparental inheritance are as diverse as the patterns (Table 1). The transmission of organelle genes to offspring can be blocked at any step in the reproductive process.

Prezygotic mechanisms eliminate organelles or organelle genomes during gametogenesis. In some organisms, the meiotic divisions produce gametes that are morphologically identical (isogamy). In others, unequal cell divisions or differential growth or both result in large maternal gametes and small paternal gametes (anisogamy or oogamy). The common but not invariant consequence is an input bias of organelle genomes in the fertilized egg that favors the female parent (Table 1, mechanism a). Alleles of an organelle gene from the paternal parent will be difficult to detect because they will be fixed by stochastic processes in a fraction $p/(m + p)$ of cells in the progeny, where p and m are the numbers of organelle genomes in the male and female gametes, respectively. The remaining cells will have no copies of the paternal allele. In the mouse, p/m is estimated to be $1–4 \times 10^{-5}$ (10). In extreme cases, organelles may be completely excluded from the gametes of one sex by unequal cytokinesis (Table 1, mechanism b); an example is the sperm of the crayfish (23). Organelles can be destroyed in the gametes (Table 1, mechanism c), as they are in the isogametes of the filamentous green alga *Temnogyra*. In another green alga, *Bryopsis*, organelle DNA disappears during the differentiation of male gametes (Table 1, mechanism d).

Other mechanisms eliminate organelles during fertilization. In some organisms (e.g., the tunicate Ascidia), sperm organelles fail to enter the egg (Table 1, mechanism e). Only nuclei are exchanged during sexual reproduction of other organisms (Table 1, mechanism f), as during conjugation of ciliated protozoa. Mechanisms b–f in Table 1 are called monogametic transmission (13).

Some zygotic mechanisms eliminate organelles from the embryo by unvarying (deterministic) processes. A striking example is the degradation of the chloroplast from the male isogamete in the filamentous algae *Spirogyra* and *Zygnema* (Table 1, mechanism g). Selective silencing (Table 1, mechanism h; ref. 24) is a process in which organelle genomes from one parent are selectively degraded in the zygote. The classic example is the enzymatic degradation of chloroplast DNA contributed by the mt^- gamete from

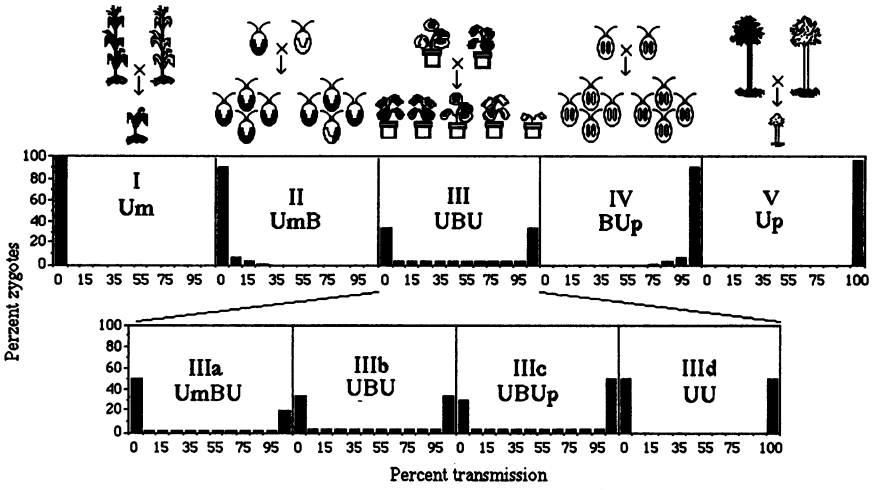

FIG. 2. Frequency distributions. The organisms and organelles are, left to right: maize chloroplasts or mitochondria (I), *Chlamydomonas reinhardtii* chloroplasts (II), geranium chloroplasts (III), *Chlamydomonas* mitochondria (IV), and sequoia chloroplasts or mitochondria (V). The lefthand parent is the female sex (maize, geranium, sequoia) or mt^+ mating type (*Chlamydomonas*). Patterns I–V contain various combinations of uniparental (U), uniparental maternal (Um or U+), uniparental paternal (Up or U−), and biparental (B) zygotes; thus, UBU is roughly equal numbers of the two types of uniparentals, plus some biparentals. The diagrams are idealized and do not precisely represent observed distributions.

Table 1. Mechanisms of uniparental inheritance

Mechanisms	Examples
Prezygotic (anisogamy/oogamy)	
a. Unequal cell divisions and differential growth produce large egg and small sperm	Mouse *Mus* M (10)
b. Exclusion of organelles from gametes during partitioning	Crayfish M (23)
c. Degradation of organelles in gamete	Green alga *Temnogyra* C (93)
d. Degradation of organelle DNA in gamete	*Bryopsis* M,C (94, 95)
Fertilization	
e. Exclusion of organelles of one parent from zygote	Tunicate *Ascidia* M (70)
f. No organelles exchanged	Ciliate *Paramecium* M (56)
Zygotic/deterministic	
g. Selective silencing/degradation of organelle	Green alga *Spirogyra* C (96)
h. Selective silencing/degradation of organelle DNA	*Chlamydomonas* C,M (33)
i. Partitioning of parental organelles into separate cells	*Cylindrocystis* C (96)
j. Exclusion of organelles from embryonic tissue	Gymnosperm *Larix* C,M (31)
Zygotic/stochastic	
k. Exclusion of organelles from embryonic tissue	Angiosperm *Pelargonium* C (25)
l. Random replication only	Yeast *Saccharomyces* M (3)

M, mitochondria; C, chloroplast.

Chlamydomonas zygotes. In another green alga, *Cylindrocystis*, the zygote contains two chloroplasts from each parent. However, these chloroplasts do not fuse or divide, and the four products of meiosis each receive one chloroplast and, hence, chloroplast genes from only one parent or the other (Table 1, mechanism i). Multicellular animals and plants have additional options because early divisions of the zygote separate embryonic and extraembryonic cells, so organelles from one parent can be eliminated by being partitioned into the extraembryonic cells (Table 1, mechanism j). For example, in the fertilized egg of the gymnosperm *Larix*, future embryonic cytoplasm is segregated into a special region that includes only paternal plastids, while a majority of mitochondria are maternal. The localization of maternal plastids in alfalfa is evidently under genetic control: high-transmitting females localize all plastids in the apical part of the unfertilized egg so that all of them enter the embryo after the first cell division, whereas some maternal plastids are localized in the basal part of the egg in low-transmitting females and are partitioned into the extraembryonic suspensor (30).

Random or stochastic processes can also eliminate organelles from the zygote or embryo (3). Organelles from different parents may segregate into embryonic and extraembryonic cells by chance (Table 1, mechanism k). This is seen in green × white crosses in *Pelargonium*, in which some very early embryos contain only white plastids, while the extraembryonic suspensor cells contain green plastids (25). This suggests that sometimes all the plastids from one parent are partitioned, by chance, into extraembryonic cells at the first and second cell divisions, leaving the embryo with chloroplasts from only one parent or the other (6). Random replication of organelle genomes may also play a role in uniparental inheritance. Organelle genomes within a cell or organelle are chosen randomly, with respect to genotype or origin, for replication. Within a zygote (or zygote clone), genomes from one parent may be replicated by chance more often than those from the other parent, or some genomes may be degraded (turnover). These processes probably play a major role in uniparental inheritance in yeast. They are all consequences of the fact that organelle genomes are relaxed, with no reinitiation block that would prevent genomes from replicating more than once per cell division. In contrast, eukaryotic nuclear genomes are stringent, having cis-acting blocks to reinitiation and consequently lacking the stochastic processes that can cause uniparental inheritance (3).

Some organisms reduce the contribution of one parent at more than one stage. In animals, for example, the sperm contribute very few mtDNA molecules to the zygote, and random replication probably reduces this contribution to zero in most individuals. Moreover, sperm mitochondria are degraded in the fertilized eggs of rodents (26–28). In the honeybee, paternal mtDNA constitutes about one-fourth of the total mtDNA in newly laid eggs because of polyspermy, but the paternal mtDNA is degraded or replicates slowly or not at all and is undetectable in larvae (29).

The diversity of mechanisms of uniparental inheritance is further demonstrated by the fact that most of these mechanisms can be found in one taxon, the seed plants (30). Moreover, mitochondria and chloroplasts can be preferentially transmitted from different parents: male and female, respectively, in some gymnosperms (31, 32); and mating types minus and plus, respectively, in *C. reinhardtii* (33).

Evolutionary History

Most Organisms Show Some Degree of Uniparental Inheritance of Mitochondria and Chloroplasts. The inheritance of organelle genes has been studied in a large number of flowering plants, one green alga, a few red algae and in a few animals, fungi, oomycetes, mycetozoa, ciliated protozoa, and plasmodia. Nearly every species produces a substantial proportion of uniparental zygotes. Exceptions are found in the yeasts *S. cerevisiae* and *Schizosaccharomyces pombe* in which some crosses produce less than 10% biparental zygotes (5). Only in some ascomycete fungi do the progeny of all zygotes receive organelle genes from both parents. Heterokaryons formed by hyphal fusions in these fungi are analogous to zygotes in that some of the parental nuclei can fuse and then undergo meiosis to produce haploid ascospores. In *Aspergillus nidulans*, mitochondrial genomes from both parents persist in all heterokaryons and recombine before they segregate into homokaryotic sectors (15, 34). This avenue of sexual reproduction might be viewed as the only exception to the rule that all organisms produce some uniparental zygotes. But the mitochondrial genes are inherited maternally, through the cleistothecial parent, in sexual crosses between heterokaryon-incompatible strains in which nuclei migrate only a short distance from each mycelium into the other (35).

Although some degree of uniparental inheritance appears to be a nearly universal phenomenon, it must be remembered that only a few species have been studied in most major groups of organisms, and only chloroplast inheritance in flowering plants has been studied in a reasonably large and diverse number of species. Moreover, there are major groups in which organelle gene inheritance has never been studied. These include the nonflowering plants; golden-brown, brown, and yellow-green algae; dinoflagellates; and most invertebrate animals. In some of these groups there is cytological evidence for uniparental inheritance (36). However, cytological data are usually not as strong as genetic data for determining the mode of inheritance of organelle genes: light microscopy may lack the resolution to identify proplastids and mitochondria in gametes or distinguish between those from different parents in the egg, the loss of fluorescent staining with DAPI or antibodies may not distinguish between loss of DNA and its dispersal, and electron microscopy is limited to very small sam-

ples of gametes or zygotes. Moreover, cytological evidence is one-sided: the absence of organelles from gametes or their destruction in zygotes is evidence for uniparental inheritance, but the presence of organelles from both parents at one stage does not demonstrate biparental inheritance because transmission may be blocked at a later stage. For these reasons, cytological data on the mode of inheritance cannot be combined with genetic data.

The Evolutionary History of Uniparental Inheritance Shows Frequent Reversals and Parallel Changes. How were the earliest mitochondria and chloroplasts inherited? One approach to this question is to deduce the answer from what we know or suspect about the organisms and their endosymbionts. Oogamy probably did not arise until well after the α-purple bacterial ancestor of mitochondria was ingested by a eukaryotic cell with no cell wall, and sexual reproduction of the host was probably initiated by fusion of whole undifferentiated cells. The resulting zygotes contained all of the endosymbionts from both cells. Initially the endosymbionts from the two gametes were indistinguishable, so that there could be no mechanism to preferentially eliminate one or the other. The host was probably unicellular, and so there could be no uniparental inheritance due to random partitioning of symbionts between embryonic and extraembryonic tissue. Uniparental zygotes would only be produced if symbionts from one parent replicated much more often than those from the other parent or were destroyed by chance; most zygotes were probably biparental. Consequently, the symbionts were probably inherited biparentally. However, it is unlikely that the endosymbiont genomes recombined because any mechanisms that the endosymbionts might have used to exchange genes while they were free-living would not work in the very different environment inside the host cytoplasm. This scenario may also apply to the cells that ingested the ancestors of chloroplasts. However, it is also possible that those cells were oogamous or anisogamous, with differentiated cells fusing to initiate sex, in which case the symbionts may have been inherited uniparentally from the beginning.

Another approach is to use phylogenetic analysis to infer the ancestral mode of inheritance from the inheritance patterns of organelles today. Figs. 3 and 4 show the most parsimonious reconstructions of the evolution of patterns of uniparental inheritance in chloroplasts and mitochondria. The pattern of chloroplast gene inheritance in the ancestor of all of the species in the chloroplast tree is equivocal because different trees with the same, minimal number of changes have different patterns (Um, UmB, UBU, or Up; see Fig. 1 for definitions) at the root. The most parsimonious reconstructions of the mitochondrial data all have strictly uniparental (maternal) inheritance at the root of that tree. However, the chloroplast and mitochondrial trees both show a great deal of homoplasy, consisting of numerous parallel evolutionary changes in the terminal branches. Unless these frequent changes in pattern began only recently, they will confound the parsimony analysis. Thus, the available data do not strongly support any ancestral pattern. The evolution of different cytological mechanisms of uniparental inheritance has not yet been subjected to phylogenetic analysis. However, most of the mechanisms described above have been observed in studies of flowering plant chloroplasts (39), and at least five different mechanisms are operating in animals (7, 8, 23, 28, 29, 36, 70, 71). It is very likely that mechanisms, as well as patterns, of uniparental inheritance have changed frequently during evolution. This observation is highly significant for evaluating evolutionary explanations of uniparental inheritance.

Evolutionary Explanations. Most animals and plants reproduce sexually at least part of the time, and this is also true of many other eukaryotes. Natural selection presumably favors biparental inheritance and recombination of nuclear genes over strictly asexual reproduction in these organisms. In contrast, most of these same organisms have reduced the proportion of biparental zygotes further, while many have eliminated them altogether, and those with biparental zygotes often have no recombination of organelle genes. Either way, the organelle genomes are effectively asexual genetic systems in sexually reproducing organisms. Why do the advantages of sexual reproduction outweigh those of asexual reproduction for nuclear genes in so many eukaryotes but not for the organelle genes? To approach this question, it is convenient and biologically reasonable to consider an organism with at least occasional sexual reproduction during which organelle genes are inherited biparentally and recombine in most zygotes (random replication will always produce some uniparental zygotes). One can then compare the consequences of losing sexual reproduction entirely, which affects both nuclear and organelle genes, to those of losing biparental inheritance or recombination of organelle genes alone. The literature on the evolutionary consequences of asexual reproduction is extensive; the following treatment relies heavily on the reviews by Kondrashov (72), Brooks (73), and others in the same volumes.

The Production of Some Uniparental Zygotes by Random Replication Is Unavoidable. We saw in the preceding section that the symbiotic ancestors of organelles were probably inherited biparentally, with few or no uniparental zygotes. As they became integrated into the cell as symbionts, their genomes lost stringent replication and partitioning. The production of some uniparental zygotes by random replication is therefore probably the primitive state. Moreover, it probably persists today in the absence of other mechanisms of uniparental inheritance (as in

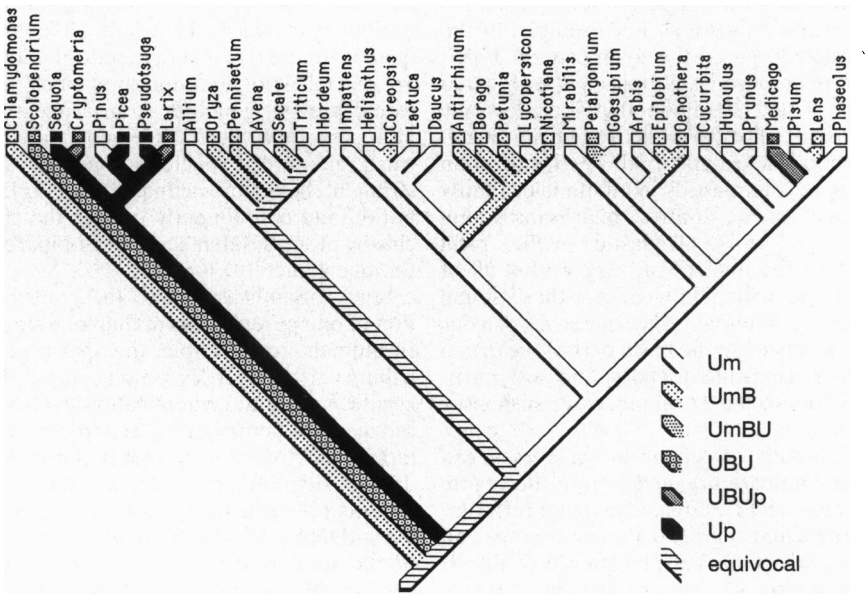

FIG. 3. Phylogenetic tree of inheritance patterns in chloroplasts. The branching pattern of the tree is based on *rbcL* sequences and on the pattern indicated in ref. 37. Each extant taxon was assigned its observed pattern of chloroplast gene inheritance (based on genetic data only), and then the ancestral nodes were assigned patterns by the parsimony algorithm of MacClade (38). Species such as *Pelargonium* show two or three different patterns but are assigned only one. Interspecific crosses that result in low viability are not included. Genetic data and references are in refs. 4, 36, 39–41 with additional data from refs. 42–45.

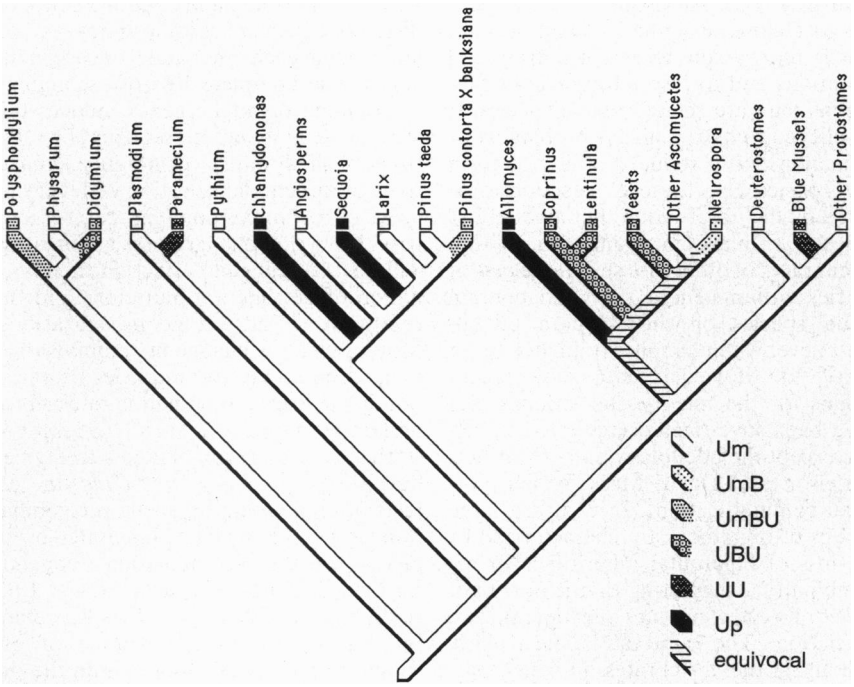

FIG. 4. Phylogenetic tree of inheritance patterns in mitochondria. The branching pattern is based mainly on 18S rRNA gene sequences (46–48), *rbcL* sequences (37), and the traditional phylogeny of the animals. Ancestral states were reconstructed as in Fig. 3. "Yeasts" = *S. cerevisiae* and *Sch. pombe*. Species such as *Saccharomyces* show two or three different patterns but are assigned only one. The low level of paternal transmission detected in interspecific crosses of *Drosophila* and *Mus* is not included, since intraspecific crosses show strictly maternal inheritance (27, 49). Genetics references are as follows: for mycetozoa, refs. 16 and 50–53; for plasmodia, refs. 54 and 55; for *Paramecium*, ref. 56; for *Pythium*, ref. 57; for *Chlamydomonas*, ref. 58; for plants, refs. 59 and 60; for fungi, refs. 3, 35, and 61–67; and for animals, refs. 7, 8, 29, 68 and 69.

yeast) or is superimposed on them, because it is biologically and evolutionarily difficult to reverse. There are only two ways to avoid producing at least a few uniparental zygotes by random replication. One is to impose stringent replication and partitioning on both the organelles and organelle genomes. This would require the acquisition of (*i*) a cis-acting mechanism to prevent replication origins from firing more than once in a cell cycle and (*ii*) a mechanism for distinguishing the sister DNA molecules produced by replication and moving them to opposite sides of the future plane of division of the cell and organelle. If there were more than one organelle per cell, there would also have to be mechanisms to ensure that each organelle divides once and one daughter organelle is partitioned to each daughter cell. This combination of evolutionary events has never been observed, and may be effectively impossible. Alternatively, the chance production of uniparental zygotes would be eliminated if both gametes had such large volumes of cytoplasm and large numbers of organelles and organelle genomes that the probability of replicating only one becomes effectively zero (order of magnitude of mutation rates), as probably happens in mycelial fusions in *Aspergillus*. But most unicellular organisms, which have small cells, and most oogamous species, which have small sperm, cannot avoid producing some uniparental zygotes by chance. The production of uniparental zygotes by random replication and partitioning is pervasive, probably because of the historical accident that it is the primitive state. But most organisms have additional mechanisms that result in even fewer biparental zygotes than expected from random replication and partitioning alone; the ubiquity of these mechanisms must be explained in terms of natural selection.

Some Advantages and Disadvantages of Sexual Reproduction Do Not Apply to Organelle Genes. Among these are the following examples. (*i*) The progeny of sexual reproduction have two parents to care for them; but organelle genes do not control parental care, so the loss of biparental inheritance or recombination of organelle genes will not affect this sometimes useful trait. (*ii*) Sexual reproduction leads to the production of resistant spores that survive harsh conditions in many organisms; but organelle genes do not control spore formation. (*iii*) Recombination in sexual diploids may facilitate the repair of chromosome damage; but organelle genomes are always present in many copies per cell, so biparental inheritance provides little additional benefit. Moreover, normal genomes can replace damaged genomes by undergoing more rounds of replication, which reduces the requirement for repair (58). On the other hand, the loss of organelle fusion would limit the number of genomes available for recombination repair, which might have a small detrimental effect. (*iv*) Repair of demethylations may occur in sexual diploids; but most organelle genomes are unmethylated, or methylation does not affect gene function. (*v*) The replacement of sexual reproduction by female parthenogenesis confers as much as a 2-fold selective advantage in many oogamous organisms by eliminating the cost of producing males; but the loss of biparental inheritance or recombination of organelles does not confer this advantage because it does not eliminate males. (*vi*) Sexual reproduction is slower than asexual because of the time required to find mates; but this does not differ for biparental and uniparental inheritance of organelles. (*vii*) Sexual reproduction has the disadvantage that it can replace more fit heterozygous genotypes by less fit homozygotes; but this is irrelevant to organelles because organelle genomes are rarely heteroplasmic.

Asexual Reproduction and Uniparental Inheritance Inhibit the Spread of Cytoplasmic Parasites. Cytoplasmic endosymbionts are common in many organisms, and these can be detrimental to their host. In a sexually reproducing organism in which the zygote receives cytoplasm from both parents, a cytoplasmic symbiont present in only one of the two parents can be inherited by all of the offspring and spread rapidly in the population when it replicates faster than the host. But when the zygote inherits cytoplasm from only one parent, the spread of detrimental cytoplasmic parasites will be limited to the cytoplasmic descendants of the cell it originally invaded. Thus, uniparental inheritance could result from selection for mutations that reduce or eliminate the cytoplasmic contribution from one parent (74). This model has been given a rigorous mathematical framework (75), which unfortunately did not include random drift.

Grun (76) proposed that uniparental inheritance would be advantageous because it reduces the spread of selfish organelle genomes that are detrimental to the organism. Examples of such genomes are the suppressive petite mitochondrial mutants in yeast and the senescence mutations in *Neurospora*. This advantage of uniparental inheritance would also apply to detrimental organelle genes as well as whole genomes and to detrimental plasmids residing in organelles. The hypothesis was explored in detail by Hastings (77), who showed that a detrimental selfish organelle genome that is inherited biparentally can increase to an equilibrium frequency that significantly reduces the population fitness. A mutant nuclear gene that causes uniparental inheritance can increase in frequency and, under some

circumstances, the entire population will become uniparental. This theory required group selection, but two models that invoke only individual selection have also been studied (78).

There are several reasons why limiting the spread of selfish symbionts or organelle DNA cannot be a general explanation of uniparental inheritance. First, a mutation causing uniparental inheritance is advantageous only when a detrimental symbiont or organelle DNA is present. Second, the detrimental genes will accumulate while the allele is being fixed, leading to very low fitness and possibly to extinction. Third, the symbiont hypothesis does not explain the many cases of uniparental inheritance in organisms with a substantial contribution of cytoplasm from both parents, including organisms such as pines and *Chlamydomonas*, where chloroplasts and mitochondria are inherited from different parents. Finally, uniparental inheritance may not be necessary to inhibit the spread of selfish organelle DNA or symbionts. Failure of organelles to fuse, as in the case of plant chloroplasts, will prevent the spread of symbionts or selfish organelle genes in organisms with biparental inheritance (36). It will also prevent the spread of selfish organelle DNA molecules, if normal and selfish DNA molecules have to be in the same chloroplast or mitochondrion to compete for replication.

The Efficiency of Natural Selection May Be Only Slightly Reduced by Uniparental Inheritance. Most of the theories about the evolutionary advantages or disadvantages of sexual reproduction focus on the fact that biparental inheritance and recombination break down linkage disequilibria that arise as a result of random drift, selection, environmental changes, or mutation. This facilitates directional or stabilizing natural selection under many circumstances (although it can be detrimental in some situations). This is because detrimental mutations may be linked to advantageous mutations, a situation called negative or repulsion linkage disequilibrium. When this happens, selection against the detrimental allele at one locus will tend to reduce the frequency of the advantageous allele at the other locus, and vice versa. Biparental inheritance and recombination will create chromosomes with two or more detrimental alleles linked to each other, and others with two or more advantageous alleles linked to each other. Then selection can reduce the frequency of the detrimental alleles and, independently, increase the frequency of the advantageous alleles.

This is the most general theory of the evolutionary advantage of sex, applying to all organisms except those that are exclusively self-fertilizing. It is essentially a group selection argument, although models invoking individual selection have also been proposed. An asexual mutant gives rise to a clone, essentially a new species, that is more likely to retain detrimental mutations and to lose advantageous mutations than are related sexual species. It is believed to have a higher probability of extinction and a reduced ability to form new species. Species-level selection is favored by the observation that asexual lineages of animals and plants usually represent races of otherwise sexual species, or species within genera that also contain sexual species, or whole genera, but almost never whole families or higher-order taxa (79). Molecular data show recent origins for the few asexual animals that have been investigated (reviewed in ref. 68), except the bdelloid rotifers (Matthew Meselson and David Mark Welch, personal communication). In contrast, large groups of organisms are characterized by the loss of biparental inheritance or recombination, suggesting that it may have little or no effect on rates of extinction and speciation. The contrast is particularly striking in the vertebrates, in which parthenogenetic species are found singly or in small genera, while nearly perfect uniparental inheritance of mitochondria is found in all the sexual species.

There are two reasons why the loss of biparental inheritance or recombination may not reduce the effectiveness of selection as much as the loss of sexual reproduction. First, organelle genotypes, and consequently organelle sex, are largely irrelevant for some kinds of natural selection. For example, organelle genes do not contribute to a host organism's resistance to parasites, nor do organelle mutations enable a parasite to overcome host resistance. Second, because the organelle genome is much smaller than the nuclear genome, its contribution to linkage disequilibria is so much smaller as to be nearly negligible. The amount of linkage disequilibrium increases with the number of polymorphic genes, and the effect of recombination on selection is larger (80). The proportion of organelle genes that are polymorphic is similar to or smaller than that of nuclear genes because the mutation rate is similar or smaller (except in primate mitochondria) and the effective population size is smaller. But the absolute number of polymorphic genes is much smaller because nuclear genomes have 100 to 1000 times as many genes as the organelle genomes in the same organism. It is likely that the complete loss of biparental inheritance (or recombination) of organelle genes will have the same effect on selection as a very modest decrease in recombination frequency of nuclear genes. Another way of looking at the problem is to calculate the average recombination frequency for all of the genes in an organism by using known values of recombination frequencies per base pair for nuclear and organelle genes on the same chromosome and counting genes on different nuclear chromosomes as unlinked from each other and from organelle genes. The complete loss of recombination among organelle genes reduces this average recombination frequency by $<1\%$ (unpublished data). Computer simulations of directional selection with varying levels of recombination (e.g., ref. 81) suggest that a 1% change in recombination will have a negligible effect on the elimination of detrimental mutations and the retention of advantageous mutations. Moreover, a 1% change in recombination is much less than the intraspecific variation in nuclear recombination rates: chromosomes from different *Drosophila* strains vary in recombination frequency by 13–14% (73). For *Drosophila*, the effects of eliminating organelle recombination altogether can be compensated by an increase in the recombination frequency for nuclear genes by a factor of 4×10^{-7} (unpublished data). It appears that eliminating biparental inheritance of organelles or recombination within the organelle genome would have a very small effect on the amount of linkage disequilibrium in a population, so long as the much larger nuclear genome is sexual and outcrossing with a high recombination frequency.

Although the contribution of the organelle genome to linkage disequilibrium may be negligible compared to that of the nuclear genome, that contribution could still potentially have serious consequences because the organelle genes play essential roles. From time to time the organelle lineages with the fewest detrimental mutations will be lost by random drift. This loss is irreversible in the absence of biparental inheritance and recombination, so the fitness of the population gradually declines. This phenomenon, called Muller's ratchet, will lead eventually to extinction (82) if it is unchecked. How have organisms with uniparental inheritance avoided this "meltdown"? First, the ratchet will move slowly or even stop entirely if many mutations are extremely detrimental, as may be the case for animal mitochondrial genomes (82). Second, when selection is soft (i.e., when the accumulation of mutations does not affect the total population size), the ratchet moves but meltdown is delayed. Third, organelle genomes are subject to intracellular and intercellular selection (83), which reduces the detrimental mutation rate measured at the level of the organism (84) (but intracellular selection is more effective with biparental than uniparental inheritance; ref. 85). Fourth, the ratchet is slowed by some but not all forms of epistasis (86, 87). These phenomena may slow the movement of the ratchet sufficiently for the organelle genomes to be rescued by low levels of biparental inheritance and recombination, by environ-

mental changes that increase their fitness, or by compensating mutations (principally in the nuclear genome because it codes for most of the organelle proteins).

If the maintenance of biparental inheritance and recombination causes only a small decrease in the effectiveness of natural selection and organisms have alternative ways of escaping extinction by Muller's ratchet, then the amount of biparental inheritance and recombination may be determined mainly by other factors. One is the presence of detrimental cytoplasmic parasites or selfish organelle DNA, as discussed above. Another is the evolution of oogamy and of extraembryonic tissues, both of which result in the production of substantial numbers of uniparental zygotes. Selective silencing in *Chlamydomonas* and some other organisms might have evolved as a mechanism for utilizing organelle DNA as a source of nucleotides during periods of starvation (58). It has also been proposed that organelle genes themselves might instigate uniparental inheritance and thereby enhance their own fitness. A mutant organelle genome could increase in frequency by causing the degradation of organelle DNA from the opposite mating type, as was proposed to explain the origin of uniparental inheritance by selective silencing in *Chlamydomonas* (88). Such mutants have been used as the starting point of models to explain the evolution of two mating types as well as of uniparental inheritance (89, 90).

It has also been shown that any difference between sexes or mating types that favors transmission of organelle genes from that sex (e.g., anisogamy with more organelle replication in the female germ line to produce large eggs), plus organelle variation favoring replication in one sex or mating type, will result in selection for organelle genomes that replicate better in the sex or mating type with stronger transmission (91). But this scenario seems unlikely to play a major role in the evolution of uniparental inheritance. There is no direct evidence for organelle variants that replicate at different rates in different sexes or mating types. This hypothesis does not explain paternal inheritance in oogamous organisms such as geraniums, alfalfa, or conifers; neither does it explain uniparental inheritance from one mating type when the mating types are similar in size and physiology.

Why Does the Evolution of Uniparental Inheritance Show so Much Homoplasy? This discussion suggests several possible explanations for the frequent changes from uniparental to biparental inheritance and back again, seen in the phylogenetic trees of Figs. 3 and 4. This kind of instability might be expected from a trait that is of little evolutionary consequence itself, and so is largely a byproduct of selection for other aspects of reproduction. Alternatively, the instability might be due to selection on the trait itself. Selection for uniparental inheritance might occur sporadically when an organism was invaded by a detrimental symbiont or when mutations produced selfish DNA or initiated a nucleocytoplasmic conflict. Uniparental lineages produced during these periods would eventually become extinct because of Muller's ratchet or other effects of the loss of recombination unless they succeeded in rescuing themselves by reacquiring biparental inheritance and recombination.

CONCLUSIONS

Uniparental and biparental inheritance are not simple alternative traits; organelle transmission is really a quantitative trait that is affected by many different molecular and cellular processes at all stages of sexual reproduction. No single mechanism explains all cases of uniparental inheritance, and no single evolutionary hypothesis can explain the great variation in extent to which organelle genes are inherited from both parents. Some generalizations can be made: nearly all of the organisms that have been studied produce at least some uniparental zygotes, and organelle genes fail to recombine in the biparental zygotes in many cases. Consequently, the benefits and costs of sexual reproduction are greatly reduced or eliminated in most organisms. The evolutionary history of organelle sex is full of reversals and parallel changes. This suggests that it is not consistently strongly advantageous (or detrimental) for species (and maybe not for individuals either). Consequently, the amount of uniparental inheritance and recombination is probably determined largely by some combination of (*i*) chance events (mutation and drift, extinction), (*ii*) changes in selection coefficients because of the presence or absence of cytoplasmic parasites, (*iii*) selection on other features (e.g., oogamy), and (*iv*) nucleocytoplasmic conflict. The forces acting on the evolutionary history of uniparental inheritance may be as diverse as those acting on sexual reproduction and as difficult to unravel. In neither case is there likely to be a single selective force of overriding importance.

How can we evaluate these hypotheses about the evolution of uniparental inheritance? First, we need to accept the likelihood that no one hypothesis is sufficient to explain the diversity of patterns of organelle gene inheritance. Second, we need more sophisticated phylogenetic analyses of the history of uniparental and biparental inheritance, including estimations of ages of uniparental and biparental lineages. Third, we need to ask the right questions. Some of the hypothetical models for the evolution of uniparental inheritance are so detailed that they are unlikely to be correct in all aspects. These need to be recast in the form of sets of mutually exclusive, exhaustive hypotheses that can be clearly distinguished by laboratory experiments or comparative analyses of natural experiments (92). Fourth, we need to identify genes that affect the transmission of organelle genes and determine how they act. Finally, here as elsewhere in evolutionary biology, we need accurate measures of the important parameters that determine the evolutionary consequences of uniparental and biparental inheritance, such as recombination frequencies and rates and selection coefficients of mutations.

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