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REVIEW

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The evolutionary processes of mitochondrial and chloroplast genomes differ from those of nuclear genomes

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Abstract This paper first introduces our present knowledge of the origin of mitochondria and chloroplasts, and the organization and inheritance patterns of their genomes, and then carries on to review the evolutionary processes influencing mitochondrial and chloroplast genomes. The differences in evolutionary phenomena between the nuclear and cytoplasmic genomes are highlighted. It is emphasized that varying inheritance patterns and copy numbers among different types of genomes, and the potential advantage achieved through the transfer of many cytoplasmic genes to the nucleus, have important implications for the evolution of nuclear, mitochondrial and chloroplast genomes. Cytoplasmic genes transferred to the nucleus have joined the more strictly controlled genetic system of the nuclear genome, including also sexual recombination, while genes retained within the cytoplasmic organelles can be involved in selection and drift processes both within and among individuals. Within-individual processes can be either intra- or intercellular. In the case of heteroplasmy, which is attributed to mutations or biparental inheritance, within-individual selection on cytoplasmic DNA may provide a mechanism by which the organism can adapt rapidly. The inheritance of cytoplasmic genomes is not universally maternal. The presence of a range of inheritance patterns indicates that different strategies have been adopted by different organisms. On the other hand, the variability occasionally observed in the inheritance mechanisms of cytoplasmic genomes reduces heritability and increases environmental components in phenotypic features and, consequently, decreases the potential for adaptive evolution.

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Introduction

Mitochondria and chloroplasts are long-term endosymbionts of eukaryotic cells. Most eukaryotic cells contain tens or hundreds of mitochondria that generate energy, and plant cells usually contain tens or hundreds of chloroplasts that carry out photosynthesis as their main function. The DNA of both mitochondria and chloroplasts encodes organelle rRNAs and, usually, tRNAs, as well as some proteins. Although cpDNA and mtDNA were at one time believed to be universally circular-mapping, their conformation and organization may actually vary considerably.

Mitochondria and chloroplasts, along with their multiple genomes, are inherited in a non-Mendelian fashion in all organisms investigated (reviewed by Birky 1995, 2001; Mogensen 1996). The strategies used in the replication and partitioning of mitochondrial and chloroplast genomes to offspring cells during mitotic and meiotic divisions are variable, while in the case of nuclear genomes one common strategy is generally used. Although there are occasional exceptions to the Mendelian transmission patterns among nuclear genomes due to meiotic drive (e.g. Lyttle 1991), opportunities for biased segregation are considerably greater among cytoplasmic genes than among nuclear genes. The inheritance of cytoplasmic genomes is often maternal but there are numerous exceptions resulting in different degrees of paternal or biparental mtDNA or cpDNA inheritance. This variety of inheritance patterns suggests that different strategies have been adopted among different organisms. The lack of a universally maternal inheritance pattern also indicates that the non-Mendelian system is unlikely to be a mere consequence of the asymmetry in the gametic size. Yet, the difference in gamete sizes may contribute to the rather commonly maternal inheritance of cytoplasmic genomes in organisms possessing gametes. Because of the variable degrees of uniparental inheritance, segregation during both mitotic and meiotic divisions, and multiple copies of genomes in each cell, evolutionary processes acting on mitochondrial and chloroplast genomes differ from those governing nuclear genomes.

This paper introduces the present knowledge of the origin, organization and inheritance of cytoplasmic genomes, and then compares the evolutionary phenomena among different types of genomes and among different organisms. The considerable variety observed in the organization and inheritance mechanisms of cytoplasmic genomes is emphasized and the presence of dynamic evolutionary changes, such as gene transfers, taking place within and among different types of genomes is described. Varying inheritance patterns and copy numbers can have important implications for the evolutionary processes of nuclear, mitochondrial and chloroplast genomes. Thus, the evolutionary features connected with each type of genome should be taken into account when conducting investigations to reveal phylogenetic relationships or population genetic structures based on DNA variation present in either nuclear, chloroplast or mitochondrial genomes.

The origin of cytoplasmic cell organelles

There have been many efforts to determine the evolutionary order of endosymbiosis and the development of the eukaryotic cell. According to Margulis (1981), mitochondria were formed before nuclei, and chloroplasts much later. On the other hand, based on the presence or absence of cytoplasmic cell organelles and gene sequence phylogenies in protists, it has been suggested that the eukaryotic cell developed first and only later did it engulf bacteria by phagocytosis to form cytoplasmic cell organelles, proteobacteria to form mitochondria more than 1.5 billion years ago, and later cyanobacteria to form chloroplasts (Cavalier-Smith 1987; Gray et al. 1999; Roger 1999). Although the view that the host cell was already eukaryotic at the time of phagocytosis is prevalent, it is not clear whether this is the correct hypothesis (Dyall et al. 2004).

The presence of regular mitochondria and chloroplasts is not universal. There are many reports on anaerobic, amitochondrial protists that either have hydrogenosomes or mitosomes, which are functional organelles derived from the original mitochondrial endosymbiont and which participate in metabolic processes but have lost their genomes (van Hoek et al. 2000; Williams et al. 2002; Tovar et al. 2003). The presence of nuclear genes of putative mitochondrial origin in those organisms provides evidence that those organisms are not primitively amitochondrial, as previously thought, but are the result of evolutionary changes after the development of mitochondrial eukaryotes. Additionally, in some plants and protists there are non-photosynthetic plastids which have lost photosynthesis but which are still involved in other metabolic processes (Lang-Unnasch et al. 1998; Fast et al. 2001).

It has been suggested that the establishment of an organelle as efficient at energy-conversion as the mitochondrion promoted the emergence of eukaryotes and allowed a major increase in genome size and complexity

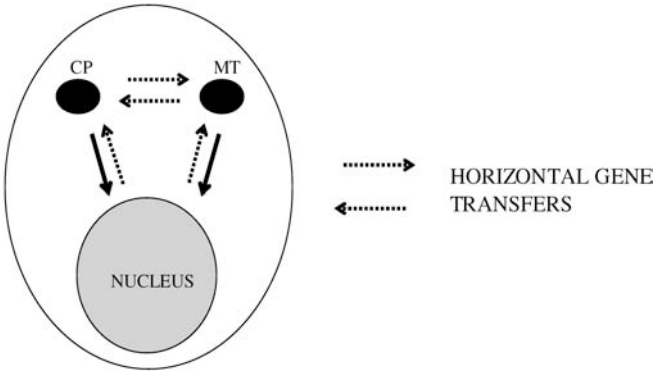

Fig. 1 Dynamic, genetic processes among cell organelles, the main direction of gene transfers being from chloroplasts and mitochondria to the nucleus

(Vellai et al. 1998). However, it is still an open question whether the symbiosis between a bacterial ancestor of a mitochondrion and a primitive eukaryotic host was indeed based on oxidative phosphorylation (Margulis 1981). Martin and Müller (1998) have proposed that the symbiosis would have arisen instead through an association between a bacterium that was able to respire but generated hydrogen as a waste product, and an anaerobic, hydrogen-dependent archaebacterium (the host).

In addition to primary endosymbiosis leading to the establishment of mitochondria and chloroplasts, there are a few known cases of secondary endosymbiosis including a eukaryote-eukaryote endosymbiosis between a phagotrophic host cell and unicellular alga which have resulted in the acquisition of a plastid (Ishida et al. 1999; Zhang et al. 2000). Reconstruction of plastid history using molecular data suggests that many algae have acquired photosynthesis through secondary endosymbiosis (Archibald and Keeling 2002). There are also reports of endosymbioses between eukaryotes and bacteria, a phenomenon common in insects (e.g. Shigenobu et al. 2000).

Of the genes present in the prokaryotic endosymbionts that became mitochondria and chloroplasts, the genes required for free-living existence were lost, most genes useful to the symbiosis were transferred to the nucleus of the host, and only some genes were retained within the organelle as a result of the dynamic DNA processes (Palmer 1997; Blanchard and Lynch 2000; Martin 2003) (Fig. 1). With the availability of the complete human genome sequence, Woischnik and Moraes (2002) performed an analysis of mtDNA pseudogene insertions in the nucleus. They detected 612 independent integrations that were evenly distributed among all chromosomes. A phylogenetic analysis of the mtDNA pseudogenes and mtDNA sequences of primates indicated a continuous transfer into the nucleus (Woischnik and Moraes 2002). Evidence for a continuous transfer of mtDNA was also detected by Mishmar et al. (2004), who analysed 247 nuclear sequences of mitochondrial origin in humans. Additionally, they discovered that the mitochondrial elements are significantly associated with repetitive nuclear elements. Such results suggest that the vicinity of trans-

posable elements influences the integration and duplication of mtDNA sequences. A mitochondrial–nuclear DNA transfer occurring de novo has been described in a human by Turner et al. (2003). In that case, a 72-bp insertion of mtDNA was transferred to the nuclear genome, causing a sporadic case of Pallister-Hall syndrome, a condition usually inherited in an autosomal dominant fashion. The transfer rate of chloroplast DNA into the nucleus has been measured experimentally by Huang et al. (2003). They integrated a nucleus-specific neomycin phosphotransferase gene (neoSTLS2) into the chloroplast genome. The screening of the progeny produced by fertilization of wild-type females with pollen from plants containing cpneoSTLS2 gave an estimate of one transposition of cpDNA to the nucleus in about 16,000 pollen grains. Such rates of DNA transfer can have significant consequences for the organization of the genome. In extreme cases, the gene transfer has already gone to completion, meaning that the organelles have lost their genomes, as discovered in some anaerobic or parasitic organisms (van Hoek et al. 2000; Fast et al. 2001; Williams et al. 2002; Tovar et al. 2003.

A proposed barrier for the usual retention of genes within mitochondria and chloroplasts is that some key integral membrane proteins of respiration and photosynthesis are very hydrophobic and are thus difficult to import across the organellar outer membranes (Claros et al. 1995; Sickmann et al. 2003). However, there are nonphotosynthetic plastids which do not encode any hydrophobic proteins at all (Palmer 1997). This shows that organelles are not fundamentally unable to import hydrophobic proteins. Other barriers may include deviations from the standard genetic code, RNA editing or finding an appropriate targeting sequence (Claros et al. 1995). In addition, it has been suggested that organelles need to be in control of the expression of genes encoding components of their electron transport chain (Allen 2003). Therefore, those components that maintain redox balance within bioenergetic membranes are synthesized where they are needed, to counteract the production and potentially deadly side effects of reactive oxygen species. On the other hand, the tendency for high AT content in chloroplast and mitochondrial genomes, and the following shift in the amino acid composition, have been suggested to be potentially deleterious to the function of some proteins (Howe et al. 2000). In that case, it would be advantageous for genes to transfer to the nucleus.

There are also cases where the gene transfer has been reversed, from the nucleus to a cytoplasmic cell organelle (Fig. 1), as suggested for the mitochondrial MSH gene (a homologue of the bacterial MutS) of the octocorals (Pont-Kingdon et al. 1998). Based on phylogenetic reconstructions, Karlberg et al. (2000) proposed that a large number of yeast mitochondrial genes have been recruited from the nuclear genome to complement the remaining genes from the bacterial ancestor. There is also evidence for DNA transfers between mitochondria and chloroplasts, such as the dispersal of chloroplast sequences throughout the rice and maize mitochondrial genomes (Nakazono and Hirai 1993; Zheng et al. 1997), and the intron transfer from the chloroplast to the mitochondrion discovered in two interfertile *Chlamydomonas* species (Turmel et al. 1993). In addition, Bergthorsson et al. (2003) have reported the presence of widespread horizontal mtDNA-to-mtDNA transfers between distantly related angiosperms, even between dicotyledons and monocotyledons. Such transfers have resulted in gene duplications and in recapture of genes previously transferred to the nucleus.

The organization of cytoplasmic genomes

The reported values of the mitochondrial DNA (mtDNA) molecule and the products encoded by its genes, as well as the genetic code, vary considerably among organisms. The size of animal mtDNA is usually 15–18 kb while yeast mtDNA is almost five times as large, and plant mtDNAs are more variable and often much larger, usually varying from 200 to 2,500 kb (Levings and Brown 1989). In the unicellular green alga, *Chlamydomonas reinhardtii*, the size of the mtDNA molecule equals only 16 kb (Gray and Boer 1988), and in protist species, the sizes of known mtDNAs vary widely, ranging from only 6 kb to over 200 kb (Gray et al. 1998). Somewhat surprisingly, there is no correlation between mtDNA size and gene content (Burger et al. 2003). The reported values of chloroplast DNA (cpDNA) molecules typically vary between 120 and 160 kb, primarily reflecting differences in the length of the inverted repeat (Palmer 1985). However, there are also very small plastid genomes, such as the 35-kb plastid genome of the non-photosynthetic malarial parasite *Plasmodium* (Wilson et al. 1996), and very large genomes, such as the 191-kb plastid genome of the red alga *Porphyra* (Reith and Munholland 1995). Besides variations in size, the gene content and even the intron content of the plastid genomes also vary considerably (Palmer and Delwiche 1998). It is notable that the genome and the DNA of an organelle might not have the same size, but the DNA may be larger than the actual genome because of the multiplicity of the genome units and the presence of replication intermediates (Oldenburg and Bendich 2004).

Both chloroplasts and mitochondria have been found to contain bacteria-derived, histone-like, structural proteins, which have a role in the organization of cpDNA and mtDNA (Kobayashi et al. 2002; Garrido et al. 2003). Such protein–DNA complexes are called nucleoids. Brewer et al. (2003) discovered in yeast that mtDNA-binding proteins are loosely packaged relative to nuclear chromatin. They also proposed that such organization may leave mtDNA accessible for transcription and replication, while making it more vulnerable to damage.

The conformation and organization of cpDNA and mtDNA may vary considerably. For instance, the mitochondrial genomes of the yeast *Saccharomyces cerevisiae* and other yeast species may be formed, at least partly, from linear multimeric molecules (Tomaska et al. 2000; Gacser et al. 2002). Some protists possess a circular-mapping mtDNA, whereas some others contain as many

as several hundred linear chromosomes (Burger et al. 2003). Lilly et al. (2001) analysed the structure and organization of cpDNA in *Arabidopsis*, tobacco and pea. They determined that both linear and circular molecules with one to a few copies were present, with monomers being the predominant structure. Incomplete genome equivalents were also detected. The results by Lilly et al. (2001) on *Arabidopsis* and later also the investigation by Oldenburg and Bendich (2004) on maize demonstrated the presence of considerable structural plasticity in the cpDNA of higher plants.

The protein products of the mitochondrial genes usually include components involved in oxidative phosphorylation, while the DNA of most plastids encodes proteins involved in photosynthesis as well as in other important metabolic processes. However, the DNA of the degenerate plastids found in non-photosynthetic plants and in parasitic protists lacks genes for photosynthesis, a feature apparently reflecting the possibility of losing genes for unused function, while retaining genes involved in gene expression (Wilson et al. 1996). In all organisms, most of the mitochondrial and chloroplast proteins are synthesized in the cytosol and then imported into the organelle. Certain proteins are encoded by nuclear DNA in one species and by organelle DNA in another, which clearly indicates the presence of gene transfer processes among different types of DNA (Palmer 1997).

The inheritance of cytoplasmic genomes

Non-maternal inheritance patterns among cytoplasmic cell organelles vary widely over various groups (Table 1) suggesting that they are more than occasional aberrations. Most of the angiosperm plants studied exhibit maternal inheritance of cpDNA, but about one-third of the genera investigated display biparental chloroplast inheritance to some degree (reviewed by Mogensen 1996). Much less is known about the inheritance of plant mtDNA, but it seems to be commonly maternally inherited. Among the well-investigated angiosperms, *Actinidia* possesses a strictly paternal inheritance of cpDNA (Testolin and Cipriani 1997), *Medicago sativa* and *Turnera ulmifolia* exhibit cpDNA inheritance ranging from predominantly paternal to predominantly maternal (Masoud et al. 1990; Shore and Triassi 1998), and *Pelargonium* expresses varying biparental inheritance patterns for both mtDNA and cpDNA (Guo and Hu 1995). Paternal leakage of mtDNA has been detected in *Cyclobalanopsis glauca* (Lin et al. 2003). Also, in the case of interspecific or intergeneric hybrids, unusual inheritance patterns of cytoplasmic genomes have been reported, e.g. the paternal inheritance of cpDNA in the genus *Larrea* (Yang et al. 2000), and the partially biparental mtDNA inheritance detected in a *Citrus–Poncirus* cross (Moreira et al. 2002). Among the gymnosperms, the conifers inherit chloroplasts exclusively or predominantly from the male parent, while the other groups (*Ephedra*, *Ginkgo*, *Zamia*) appear to have maternal chloroplast inheritance (reviewed by Mogensen 1996). Mitochondria are inherited either maternally, paternally or biparentally, depending on the group of gymnosperms. However, in *Chamaecyparis obtusa* (Cupressaceae) considerable maternal leakage and heteroplasmy of cpDNA has been reported (Shiraishi et al. 2001).

There is very limited information regarding the inheritance patterns of mtDNA and cpDNA in pteridophytes, but there is an indication that the inheritance of cpDNA is maternal (Gastony and Yatskievych 1992; Guillon and Raquin 2000). Inheritance patterns in the green alga *Chlamydomonas reinhardtii*, which has cells of two mating types, have been studied in many investigations. The results show that the inheritance of cpDNA is generally uniparental and under the direct control of the nuclear genome (Nishimura et al. 2002). Among fungi, the yeast mitochondria and their genomes and gene expression have been investigated extensively. The inheritance of fungal mtDNA is uniparental, biparental or mixed uniparental/biparental, depending on the organism, and there is also evidence of the influence of the nuclear genome on the inheritance patterns (Birky et al. 1978; Dujon 1981; Takano 2000; Yan and Xu 2003). In addition, several mutations, which influence the mitochondrial transport and maintenance, have been found and described in yeast (e.g. Gurvitz et al. 2002).

In animals, mitochondrial genomes are mainly maternally inherited with occasional paternal leakage or more regular paternal inheritance (Gyllensten et al. 1991; Kondo et al. 1992; Magoulas and Zouros 1993; Hagelberg et al. 1999; Behura et al. 2001; Jannotti-Passos et al. 2001; Schwartz and Vissing 2002, 2003; Kvist et al. 2003; Kraytsberg et al. 2004). Sometimes paternal leakage can be considerable. Schwartz and Vissing (2002) detected in an adult human that 90% of the mtDNA of skeletal muscle was paternally derived. The situation may have resulted from incomplete destruction of paternal mtDNA and its replicative advantage in cells with a high energy demand. Paternal mtDNA was not detected in other types of cells.

Some paternal leakage is almost inevitable to occur when there is sperm penetration. However, what matters is whether paternal organelles survive long enough to be established in the sperm line of the next generation. The mussel genus *Mytilus* is a well-studied case regularly expressing an unusual inheritance of mitochondria: Females carry predominantly maternal mtDNA, while males carry maternal mtDNA in their somatic tissues and paternal mtDNA in their gonads (Zouros et al. 1994; Ladoukakis et al. 2002; Cao et al. 2004). The mechanism responsible for this phenomenon, called doubly uniparental inheritance, has been demonstrated in *M. edulis* (Cao et al. 2004): in embryos from females that produce only daughters, sperm mitochondria aggregate and end up in one blastomere in the two- and four-cell stages. Cao et al. (2004) have postulated that the mitochondrial aggregate eventually ends up in the first germ cells. This would explain the presence of paternal mtDNA in the male gonad. Also, the clam *Tapes philippinarum* has been found

Table 1 Examples of non-maternal inheritance of cytoplasmic genomes

Group	Genome	Mode of inheritance	Reference
Fungi			
Ascomycota			
Saccharomyces	mtDNA	Biparental	Dujon 1981
Basidiomycota			
Coprinus	mtDNA	Biparental	May and Taylor 1988
Myxomycota			
Physarium	mtDNA	Maternal, biparental	Takano 2000
Plantae			
Gymnospermae			
Araucariaceae	cpDNA, mtDNA	Paternal	Mogensen 1996
Cephalotaxaceae	cpDNA, mtDNA	Paternal	Mogensen 1996
Cupressaceae	cpDNA	Paternal, biparental	Mogensen 1996; Shiraishi et al. 2001
	mtDNA	Paternal	Mogensen 1996
Pinaceae	cpDNA	Paternal	Mogensen 1996
	mtDNA	Maternal, biparental	Brums and Owens 2000
Taxaceae	cpDNA	Paternal	Mogensen 1996
Taxodiaceae	cpDNA, mtDNA paternal		
Angiospermae			
Actinidia	cpDNA	Paternal	Testolin and Cipriani 1997
Brassica	mtDNA	Paternal leakage	Erickson and Kemble 1993
Coreopsis	cpDNA	Paternal leakage	Mason et al. 1994
Cyclobalanopsis	mtDNA	Paternal leakage	Lin et al. 2003
Lens	cpDNA, mtDNA	Paternal leakage	Rajora and Mahon 1994, 1995
Liriodendron	cpDNA	Paternal leakage	Sewell et al. 1993
Magnolia	cpDNA	Paternal leakage	Sewell et al. 1993
Medicago	cpDNA	Maternal, paternal, Biparental	Masoud et al. 1990
Musa	mtDNA	Paternal	Fauré et al. 1994
Pelargonium	cpDNA, mtDNA	Biparental	Guo and Hu 1995
Rhododendron	cpDNA	Biparental	Noguchi 1932
Secale	cpDNA, mtDNA	Biparental	Soliman et al. 1987
Stellaria	cpDNA	Paternal leakage	Chong et al. 1994
Turnera	cpDNA	Maternal, paternal, Biparental	Shore and Triassi 1998
Animalia			
Arthropoda			
Drosophila	mtDNA	Paternal leakage (0.1%)	Kondo et al.1992
Orseolia	mtDNA	Maternal, paternal	Behura et al. 2001
Mollusca			
Mytilus	mtDNA	Doubly uniparental	Zouros et al. 1994; Ladoukakis et al. 2002; Cao et al. 2004
Tapes	mtDNA	Doubly uniparental	Passamonti and Scali 2001
Platyhelminthes			
Schistosoma	mtDNA	Paternal	Jannotti-Passos et al. 2001
Chordata			
Engraulis	mtDNA	Paternal leakage (0.7%)	Magoulas and Zouros 1993
Parus	mtDNA	Paternal leakage	Kvist et al. 2003
Mus	mtDNA	Paternal leakage (0.01–0.1%)	Gyllensten et al. 1991
Homo	mtDNA	Paternal leakage	Hagelberg et al. 1999; Schwartz and Vissing 2002

to possess a doubly uniparental mechanism for the inheritance of mtDNA (Passamonti and Scali 2001).

There is a surprising variety of mechanisms by which cytoplasmic cell organelles are, or are not, transmitted to the offspring. The mechanisms resulting in the suppression of male cytoplasmic inheritance in seed plants include the exclusion or loss of cytoplasmic organelles from the generative cells or sperm cells, the exclusion of the male cytoplasm at the gametic fusion, and the degradation of the organelle DNA within the generative and/or sperm cells (Mogensen 1996; Nagata et al. 1999). In the case of maternal elimination, there may be a transformation of the cytoplasmic organelles along with their distribution away from the egg/zygote nucleus or their degeneration soon after the gametic fusion (Mogensen 1996; Brums and Owens 2000). However, none of these elimination mechanisms are perfectly effective in every instance.

In the green alga *Chlamydomonas reinhardtii,* a typical feature of the early zygote development is the active selective degradation of cpDNA from the mating type minus parent (Nishimura et al. 2002). It is proposed that there is a mating-type plus-specific nuclease that is activated in mating-type plus gametes and participates in the destruction of mating-type minus cpDNA in young zygotes, thereby ensuring uniparental inheritance of cpDNA (Nishimura et al. 2002). In the honeybee, *Apis mellifera*, the male contribution of mtDNA represents up to 27% of the total mtDNA in the fertilized eggs 12 h after oviposition. However, during subsequent developmental stages, the proportion of paternal mtDNA slowly decreases until

the hatching of the larvae, at which point only traces are found (Meusel and Moritz 1993). In experimental human cell cultures, mitochondria in sperm can enter somatic cells relatively easily, but there seem to exist mechanisms to eliminate sperm-derived mtDNA from somatic cells (Manfredi et al. 1997). In the fertilized oocyte, it has been actually shown that the sperm mitochondria are subjected to upiquitin-dependent proteolysis during spermatogenesis and following elimination during pre-implantation development (Sutovsky et al. 2000). One of possibly several other mechanisms preventing paternal mtDNA transmission in mammals is the downregulation of the mitochondrial transmission factor A (T_{fam}) and mtDNA copy number during spermatogenesis (Rantanen et al. 2001). The importance of nuclear background and the presence of a species-specific recognition system for the destruction of sperm mitochondria have been shown by Sutovsky et al. (2000), who found that the ubiquitination otherwise observed in sperm mitochondria is not seen in hybrid embryos between domestic cow eggs and sperm of wild cattle. Similarly, Kaneda et al. (1995) detected that in intraspecific hybrids of *Mus musculus*, the paternal mtDNA disappeared after the pronucleus stage, while in interspecific hybrids between *M. musculus* and *M. spretus*, paternal mtDNA was detectable from the pronucleus stage to the newborn mouse. More recently it has been observed in mouse eggs that mitochondria from spermatids, but not from liver, are selectively eliminated, which emphasizes the uniqueness of sperm mitochondria (Shitara et al. 2000). Kvist et al. (2003) discovered that among 27 birds sampled in a zone where two subspecies of the great tit (*Parus major*) live, one bird of the major phenotype possessed both minor and major mitochondrial haplotypes and it was assumed that this heteroplasmy had resulted from mtDNA leakage from the bird's father or from paternal leakage in previous generations. As the knowledge of the importance of nuclear background for the inheritance of cytoplasmic genomes increases, it becomes possible that this may not have been a random aberration but, alternatively, may have been caused by a partial failure to recognize the system for the destruction of sperm mitochondria in a bird hybrid between two subspecies.

The evolutionary processes of cytoplasmic genomes

Mutations

To establish a nuclear copy of an originally mitochondrial or chloroplast gene is a complex process, which has had varying rates of occurrence in different eukaryotic lineages (Blanchard and Lynch 2000). At the moment, there is no satisfactory answer for the transfer of organellar genes. A decreased mutation rate has been suggested as a potential selective advantage of the movement of genes from cytoplasmic cell organelles to the nucleus. Chloroplasts and mitochondria have high rates of redox reactions, producing oxygen-free radicals that chemically modify DNA. The possibility of such mutations, coupled with rather loosely packed structural proteins in the cytoplasmic nucleoids, may cause a disruption in the proper function of organelle DNA (Allen and Raven 1996; Brewer et al. 2003). Indeed, cytoplasmic DNA has been shown to be more prone to damage than nuclear DNA (Mambo et al. 2003). Yet, cpDNA and mtDNA both have their own repair systems (Prina 1996; Ling et al. 2000).

Although the idea that a decreased mutation rate is a factor causing the transfer of organelle genes to the nucleus is an attractive hypothesis, it does not seem to be generally correct. Based on investigations on the sequence divergence in different cell organelles, it has been discovered that in vertebrates the evolutionary rates are higher in mitochondrial genomes than in nuclear genomes, while in most invertebrates the evolutionary rates of mitochondrial and nuclear genomes are quite similar (Gray 1989; Crawford 2003). However, Moriyama and Powell (1997) discovered that in *Drosophila* the mitochondrial genes have 1.7–3.4 times higher synonymous substitution rates than the fastest evolving nuclear genes, and 4.5–9.0 times higher rates than the average nuclear genes. Plant mitochondrial genomes evolve significantly less rapidly than do the nuclear genomes, while chloroplast genomes evolve at a rate somewhat between these two (reviewed by Gray 1989). These results also indicate that DNA present in cytoplasmic genomes is not necessarily the target of extensive mutations when compared with nuclear DNA. However, Allen and Raven (1996) have emphasized the importance of making a clear distinction between mutation frequency and evolutionary rate. Potentially, a high mutation frequency may result in a slow evolutionary divergence if the selection pressure maintaining the original sequences is strong. This could be true in the case of nonsynonymous mutations, and even in the case of synonymous mutations if there are codon preferences.

In the case of the uniparental inheritance of chloroplasts and mitochondria, mutations in cpDNA and mtDNA have different consequences for each sex. If inheritance is maternal, cytoplasmic mutations that increase male fitness are not rewarded by increased representation among progeny, while mutations that have male-limited deleterious effects may be maintained in the population. In the extreme case, such behaviour among the cytoplasmic genomes could result in skewed sex ratios and, eventually, in species extinction or, perhaps, in the evolution of parthenogenesis through the continued production of females alone (Avise 1998). However, biparental cytoplasmic inheritance would potentially produce competition among the many copies of cytoplasmic genomes, while uniparental inheritance may provide a means of avoiding conflict between different organelle genomes present within the zygote (Eberhard 1980). It has been proposed that genetic conflicts may be a central force in the evolution of genetic systems, including inheritance patterns (Hurst et al. 1996).

Mitochondrial mutations, which have been investigated widely in humans, are associated with a range of degenerative conditions, including blindness caused by

Leber's hereditary optic neuropathy, various muscle and heart conditions in maternally inherited myopathy and cardiomyopathy, Parkinson's and Alzheimer's diseases, cancer, and reduced sperm motility and male infertility due to the damaged mitochondrial energy sources (Frank and Hurst 1996; Wallace 1999; Mambo et al. 2003). Many of the somatic mtDNA mutations in human cancers are located in the D-loop and especially in its D310 region. Using induced mutations, Mambo et al. (2003) have shown that the D-loop, indeed, is highly susceptible to mutations because of its vulnerability to DNA damage and relatively inefficient repair mechanisms. Additionally, a group of mitochondrial disorders found in humans are diseases caused by nuclear genes that affect the stability of mtDNA (Suomalainen and Kaukonen 2001). In these disorders, a nuclear gene defect causes secondary mtDNA loss or deletion. The diseases resulting from such an interaction between nuclear and mitochondrial genomes clinically resemble those caused by mtDNA mutations but follow a Mendelian inheritance pattern. The presence of mutations in mtDNA is not the only source of mtDNA-based abnormalities, as May-Panloup et al. (2003) have reported a connection between a very high mtDNA content and male infertility in humans. Besides humans, which have been the target of extensive investigations, male sterility attributable to mutations in cytoplasmic cell organelles is common in insects and also in plants, although the effects of the male sterility mutations are then often compensated by the evolution of nuclear suppression alleles that restore male fertility (Hurst et al. 1996; Avise 1998).

In an investigation on the inheritance pattern of longevity, a significant genetic maternal component in human life-span has been detected (Korpelainen 1999). This discovery is in accordance with the mitochondrial theory of ageing, which has been supported by the discovery that mitochondrial function declines and mtDNA mutations, predominantly in brain and heart muscle, increase in an age-dependent manner (Chomyn and Attardi 2003), and with the hypothesis that longevity requires particular interactions between mtDNA and nuclear DNA (De Benedictis et al. 2000). The increasing accumulation of mutations with age has been attributed to several factors, which contribute to the mutation rate, such as slipped mispairing, topoisomerase cleavage, the absence of excision repair, and incomplete repair of damage caused by free radicals produced as a by-product of oxidative phosphorylation (Wei and Lee 2002). Although most mitochondrial mutations are somatic and not inherited, there are apparently differences between individuals in the occurrence of germ-line mutations, in the susceptibility of mtDNA to damage during life, or in the general function of mitochondria (Korpelainen 1999).

Recombination

The lack of sexual recombination may be a cause of the transfer of genes from chloroplasts and mitochondria to the nucleus. The evolutionary advantage of sexual recombination as a means of creating a wide range of gene combinations is well documented. However, heteroplasmy resulting from mutations, biparental inheritance, or exchange with nuclear pseudogenes of mitochondrial origin could provide the potential for recombination among different genomes both within and between cytoplasmic cell organelles. The presence of intergenomic mtDNA recombination has been shown in laboratory experiments in fungi (Toth et al. 1998), in algae (Remacle et al. 1995), in somatic hybrid plants (Moriguchi et al. 1997), in plants regenerated from embryogenic callus cultures (Weigel et al. 1995) and in protoplast-derived plants (Albert et al. 2003). Although the evidence from natural populations is limited, the presence of mtDNA recombination has been shown in natural populations of the fungi *Armillaria gallica* and *Candida albicans* (Saville et al. 1998; Anderson et al. 2001), and also in the gynodioecious plant *Silene acaulis* (Staedler and Delph 2002). Contrary to earlier expectations (Birky 2001), such processes operate at a low rate on animal mtDNA as well, as shown in the nematode *Meloidogyne javanica*, in the mussels *Mytilus galloprovincialis* and *M. trossulus*, in the flounder *Platichthys flesus*, and in humans (Lunt and Hyman 1997; Eyre-Walker et al. 1999; Hagelberg et al. 1999; Ladoukakis and Zouros 2001; Hoarau et al. 2002; Burzynski et al. 2003; Kraytsberg et al. 2004). However, Elson et al. (2001) claim that mtDNA recombination is not sufficiently frequent to overturn the standard paradigm that mtDNA is maternally inherited and the mtDNA lineages are clonal. Intergenomic cpDNA recombination has been discovered in interspecific algal hybrids, in the protist *Crypthecodinium cohnii* and in the bean *Vigna angularis* (Lemieux et al. 1981; Kato et al. 2000; Norman and Gray 2001).

In all, intergenomic recombination appears to be a relatively infrequent phenomenon in cytoplasmic cell organelles and there is very little proven evidence of its presence. It has been proposed that recombination may actually serve as a part of an mtDNA repair system (Mason et al. 2003). It follows that heteroplasmy usually accumulates without significant reorganization of the genomes through intergenomic recombination and, consequently, inheritance is effectively asexual. Yet, when inferring phylogenies based on cytoplasmic genomes or when studying human mtDNA-associated diseases, the possibility of recombination, deviations from strictly uniparental inheritance, and possible discrepancies in mtDNA and cpDNA molecular clocks should not be neglected.

Selection

Genes in cytoplasmic cell organelles can be subject to considerable selection both within and among individuals. In nuclear genes, selection is mostly limited to taking place among individuals only, although there are exceptions, such as cancer cells. A requirement for selection

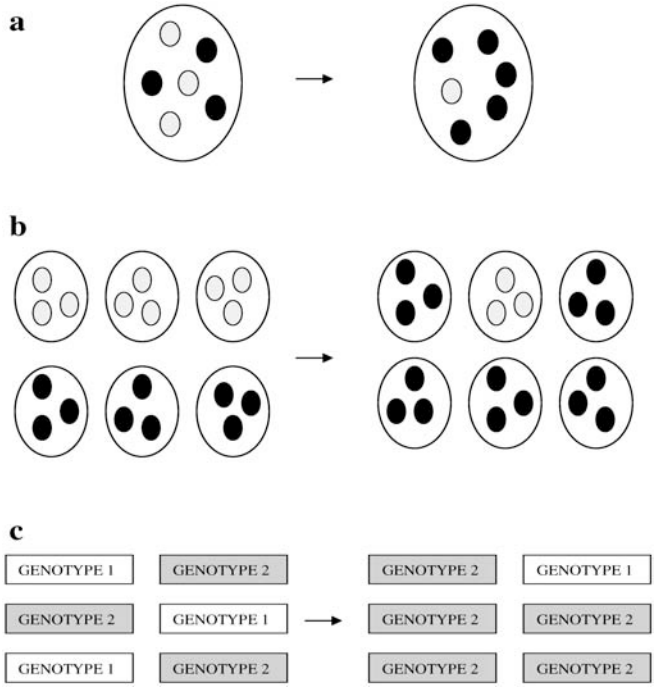

Fig. 2 Selection at three levels: **a** cytoplasmic genomes with intracellular heteroplasmy, intracellular selection; **b** cytoplasmic genomes with intercellular heteroplasmy, intercellular selection; **c** nuclear genomes, genetic variation among individuals, selection among individuals

within individuals is the presence of different mitochondrial or chloroplast genomes, heteroplasmy, which can be attributed to mutations or biparental inheritance. Selection, as also genetic drift, within individuals in cytoplasmic organelles can be either intracellular (among organelles within a cell, intracellular heteroplasmy required) or intercellular (among cells within an individual, intercellular heteroplasmy required) (Fig. 2) or a combination of both. The effect of intracellular selection among the multiple genomes is complex. Intracellular selection combined with drift means that multiple genomes can not hide recessive mutations long and, consequently, detrimental mutations will be lost (Birky 1991). Unfortunately, the reported studies only rarely distinguish intracellular and intercellular selection.

Such additional levels of selection present in cytoplasmic genomes have the potential for environmentally induced selective changes in gene frequencies even within the life-span of an individual and it can provide a mechanism for very rapid evolution, as discovered, for instance, in *Senecio vulgaris* for the resistance to triazine herbicides caused by a point mutation in the chloroplast genome (Frey 1999). The presence of intracellular selection among mitochondrial genomes was shown already in the 1970s in *Paramecium* (Adoutte and Beisson 1972) and yeast (Birky 1973), which are unicellular organisms and cannot be subject to intercellular selection within individuals. The presence of selection among mitochondrial genomes within cells has been suggested in protoplast-derived *Nicotiana sylvestris*, which has mitochondrial heteroplasmy apparently resulting from recombination (Albert et al. 2003). Ballard and Whitlock (2004) have reviewed recent evidence for the presence of both direct and indirect selection influencing mtDNA. Because there is generally very little or no recombination in mtDNA, selection at one nucleotide affects indirectly the whole molecule.

The presence of selection among mitochondrial genomes has been clearly demonstrated in heteroplasmic *Drosophila* (De Stordeur 1997). After cytoplasm microinjections between eggs of different *Drosophila* lineages carrying varying mtDNA types, the processes involved in the evolution of heteroplasmic states were strongly affected by the selective values of the different mtDNA types. In tests for selection on mtDNA variants and for the effects of nuclear–cytoplasmic interactions involving crosses in *Drosophila*, it was discovered that different mtDNA variants were favoured, depending on the nuclear background (Nigro 1994; Sackton et al. 2003). In embryos derived by nuclear-transfer, the fusion of the donor cell and recipient oocyte can cause heteroplasmy. Takeda et al. (2003) detected in nuclear-transfer calves donor mitochondria immediately after the fusion and they observed that the donor-derived mtDNAs possessed a significant replicative advantage over recipient mtDNAs during the course of embryogenesis. Using an experimental set-up, Casane and Gueride (2002) investigated the dynamics of mtDNA length polymorphisms in several rabbit cell clones containing different proportions of two mtDNA molecular types. The results showed that there was a tendency for mtDNA molecules with a longer array of repeats to have a replicative advantage that could depend on the nuclear background.

In heteroplasmic mice, Jenuth et al. (1997) have found evidence for random segregation in some tissues, but in others strong tissue-specific and age-related selection for different mtDNA genotypes is present in the same animal. Such results indicate the influence of tissue-specific expression of nuclear genes in the interaction between the nuclear and mitochondrial genomes. Comparably, diversification and shifts of mitochondrial heteroplasmy observed in human cell lines have been interpreted as being under nuclear genetic control (Lehtinen et al. 2000). On the other hand, investigations on the mussel *Mytilus trossulus* show that selection acting on mtDNA is largely independent of the nuclear genome (Quesada et al. 1999), and the pattern of mtDNA differentiation detected in *M. edulis* is explained well by the nearly neutral theory of evolution giving roles also to selection, drift and mutation (Skibinski et al. 1999).

Blier et al. (2001) have suggested that selection is actually expected in the case of mtDNA, since the proteins encoded by mtDNA interact with many peptides encoded in the nucleus to form the mitochondrial electron transport system (ETS). The ETS is the primary energy generation system, and natural selection would be expected to favour mutations that enhance its function. Those mutations could occur in both mitochondrial and nuclear genes and lead to intergenomic co-adaptation.

Evidence for deviations from neutrality is given by Elson et al. (2004) who assessed selection in 560 mtDNA coding-region sequences in humans. Although selection was not indicated by all tests, the apparent presence of selection and also gene-specific and lineage-specific variation in selection patterns were discovered. Evidence for purifying and adaptive selection in human mtDNA is also provided by Ruiz-Pesini et al. (2004), who analysed 1125 mtDNA sequences and concluded that specific mtDNA replacement mutations have influenced the adaptation of humans. On the other hand, a situation representing a neutral polymorphism is heteroplasmy involving mtDNAs with mutations for Leber hereditary optic neuropathy and wild-type mtDNAs, as shown by Puomila et al. (2002), based on a study conducted over a period of 4–12 years for heteroplasmic individuals.

Genetic drift

Cytoplasmic genomes are potentially subject to random drift effects both within (intra- or intercellular) and among individuals. A great difference when compared with nuclear genomes is that nuclear genes in a germ cell lineage during meiosis pass through a stage with one molecule per gamete while cytoplasmic genomes are usually transmitted in multiple copies both in mitosis and meiosis. However, because of sexual recombination and mixing of male and female genes, the drift of the nuclear genes reflects the effective size of their population. Yet, based on the suggested theories (e.g. Birky et al. 1989), there may be a chance for a bottleneck and considerable genetic drift among uniparentally transmitted mitochondrial and chloroplast genomes. In a genetic study on the seal *Mirounga leonina*, Slade et al. (1998) estimated that the rate of genetic drift for mtDNA is twice the rate for nuclear DNA. When studying natural populations of *Pinus ponderosa*, Latta et al. (2001) detected a pattern of cpDNA and mtDNA variation, which reflects the action of genetic drift. Although the overall magnitude of drift effects was somewhat greater for maternally inherited mtDNA than for paternally inherited cpDNA, the observed disequilibria indicate that both the number of seed and pollen parents are limited in *P. ponderosa* (Latta et al. 2001). Drift-caused effects have been detected also in the cpDNA of *Olea europaea* (Besnard et al. 2002) and in the mtDNA of human primary oocytes (Brown et al. 2001).

In order to examine mitochondrial bottlenecks, Bergstrom and Pritchard (1998) have developed a model which shows that a bottleneck increases the efficacy of selection against deleterious mitochondrial mutations by increasing the variance in fitness among the eukaryotic hosts. As a consequence, a bottleneck may lead to improved mitochondrial performance instead of evolutionary degradation. The model may be applied to the evolution of chloroplasts as well.

Genetic differentiation

As expected based on the theory dealing with genetic differentiation for uniparentally inherited organelle genes (Birky et al. 1989; McCauley 1995; Hu and Ennos 1999), investigations in seed plants demonstrate greater genetic differentiation for both maternally transmitted cpDNA and mtDNA, which migrate solely by seed, and for paternally transmitted genomes, which migrate by pollen, than for nuclear genomes, which are dispersed by both pollen and seed (McCauley 1994; Tomaru et al. 1998). As well as the differences in the rates of migration among different genomes, it is notable that the uniparental mode of inheritance reduces the local effective population size, relative to the nuclear genes. It follows that such differences in the effective population sizes also contribute to the disparity in genetic differentiation between genomes (McCauley 1995).

In *Pinus sylvestris*, for example, the estimates of F_{ST} (the proportion of total variability due to differences among populations) for the maternally transmitted mtDNA and for the biparentally transmitted nuclear DNA equalled 0.370 and 0.028, respectively (Sinclair et al. 1998), and the estimates for the maternally transmitted mtDNA and the nuclear allozyme loci in *Fagus crenata* were 0.963 and 0.039, respectively (Tomaru et al. 1998). This reflects the considerably greater migration occurring among nuclear genomes. Comparably, the estimates of F_{ST} for the paternally transmitted cpDNA and for the nuclear DNA in *Picea glauca* equalled 0.147 and 0.037, respectively (Furnier and Stine 1995), and the estimates of F_{ST} for the maternally transmitted cpDNA and the nuclear allozyme loci in *Silene alba* were 0.67 and 0.13, respectively (McCauley 1994). Sequence and restriction site analyses conducted for both cpDNA and mtDNA in *Pinus densata* revealed that population differentiation is high based on the paternally inherited cpDNA (0.533) and even higher based on the maternally inherited mtDNA (0.905) (Song et al. 2003). Also in *P. pinaster*, the level of population differentiation was found to be higher based on mtDNA than that based on cpDNA (Burban and Petit 2003). The observed differences in the estimates of genetic differentiation between different types of genomes clearly show that both seeds and pollen contribute significantly to gene flow in seed plants.

In accordance with several plant studies, the unisexually (maternally) inherited mtDNA of humans also exhibits more interpopulation heterogeneity (0.13–0.39) than does the nuclear DNA (0.05–012) (Merriwether et al. 1991; Koji et al. 1998). The mussels of the genus *Mytilus* possess a doubly uniparental inheritance of mtDNA. When the mtDNA variation was investigated in *M. galloprovincialis*, which has two types of mtDNA genomes, the maternally transmitted F type and the paternally transmitted M type, it was discovered that the M genome evolves at a higher rate than the F genome (Ladoukakis et al. 2002). The occasional invasion of the F-type mtDNA to the paternal transmission route influences the composition of paternally transmitted mtDNA. Therefore, the

two types of mtDNA provide different results if used to reveal information for population and phylogenetic studies in mussels (Ladoukakis et al. 2002).

Conclusions

The tremendous transfer of genes from the cytoplasmic cell organelles to the nucleus that has taken place during evolution following the endosymbiosis between the eukaryotic or pre-eukaryotic cell and the bacteria which formed mitochondria and chloroplasts present in eukaryotic cells may indicate an evolutionary advantage to nuclear genomes. Yet, the fact that there are still genes remaining in the cytoplasmic genomes shows that mitochondrial and chloroplast genomes can be maintained in the course of evolution.

Table 2 summarizes the evolutionary processes at the cell and individual levels in nuclear genomes and in the genomes of cytoplasmic cell organelles. The greatest differences in the evolutionary processes between the nuclear genomes and the genomes of cytoplasmic cell organelles are that in multiple-copied cytoplasmic genomes, selection and drift do not operate just at the individual level but also at the cell level, and that intermolecular recombination is of limited importance, whereas mutations are in the range of their frequency in nuclear genomes. However, the presence of even a low rate of recombination, which has been reported in a few cases, may have an important genetic contribution to cpDNA and mtDNA lineages and, consequently, to the estimates of the time of divergence of different cpDNA and mtDNA types. A model related to the unique feature that cytoplasmic genomes usually have multiple copies has been presented by Sears and Vanwinkle-Swift (1994), who have developed the salvage/turnover/repair (STOR) model for chloroplast inheritance in *Chlamydomonas* algae. The model focuses on organelle DNA turnover as a source of sustenance for the cell during periods of starvation. It proposes that as a consequence of the high ploidy of the chloroplast genomes, many copies are dispensable and their degradation would provide nucleotides for recombination, repair, RNA synthesis and cell metabolism.

Table 2 Evolutionary processes at the cell and individual level in the nuclear genomes and in the genomes of the cytoplasmic cell organelles

	Genome type	
Evolutionary unit	Nuclear	Cytoplasmic
Cell	Mutation	Mutation
(within and among cells)		Selection
		Drift
		Recombination (rare)
Individual	Selection	Selection
(among individuals)	Drift	Drift
	Migration	Migration
	Recombination	Recombination (rare)

The replication and partitioning of the multiple-copied mitochondrial and chloroplast genomes to offspring cells at cell division occur in a more flexible manner when compared to nuclear genomes. This potentially allows rapid evolution following effective selection and adaptation within individuals, as also indicated by the models by Birky (1991) and Bergstrom and Pritchard (1998). On the other hand, the same multiple-copy organization may prove to be a disadvantage if it allows unfavourable cytoplasmic genes to spread in the population. In some cases this may result from conflicts between nuclear and cytoplasmic genes, or from a unisexual inheritance pattern, if cytoplasmic genotypes have different consequences on each sex.

Potential reasons for the non-Mendelian, often uniparental, inheritance of cytoplasmic genomes include specialization to replicate only in one type of a germ-line (Godelle and Reboud 1995), competitive advantage at fertilization for sperm that has minimized its organelle content (Keys et al. 1995), and the prevention of any incompatibilities between cytoplasmic genomes and between cytoplasmic and nuclear genomes (Eberhard 1980). In plants, maternal inheritance might be advantageous because aggressive, deleterious cytoplasmic genes would be transmitted through pollen more widely than similar genes through seeds (Grun 1976), or maternal inheritance may have evolved as a mechanism that prevents foreign or pathogenic DNA from entering the egg, and organelles of males may belong to this category (Coleman 1982).

The two main questions concerning the evolution of cytoplasmic cell organelles concern the genetic composition of mitochondria and chloroplasts (why most genes have been lost or transferred to the nucleus, but some genes simply remain in the cytoplasmic genomes) and their inheritance patterns (why they are often, but not universally, maternally inherited). Although there is a fair amount of information of processes and potential advantages associated with evolutionary phenomena in different types of genomes, the situation is still far from being fully resolved. A potential problem concerns the variability occasionally observed in the inheritance of cytoplasmic genomes. Such variability reduces heritability and, consequently, the potential for adaptive evolution. An additional question that needs to be examined in future research is the extent of the effect the nuclear genome has on cytoplasmic gene expression, and how selection might act on such nuclear modifiers.

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