CRITICAL REVIEWS IN PLANT SCIENCES
https://doi.org/10.1080/07352689.2017.1327762

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Plant Mitochondrial Genome Evolution and Cytoplasmic Male Sterility

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ABSTRACT

Mitochondria are responsible for providing energy currency to life processes in the molecular form of ATP and are therefore typically referred to as the power factories of cells. Plant mitochondria are also relevant to the common phenomenon of cytoplasmic male sterility, which is agronomically important in various crop species. Cytoplasmic male sterility (CMS) is a complex trait that may be influenced by patterns of mitochondrial genome evolution, and by intergenomic gene transfer among the organellar and nuclear compartments of plant cells. Here, we review patterns and processes that shape plant mitochondrial genomes, some relevant interactions between organelles, and the general features shared by the majority of cytoplasmic male-sterile genes in plants to further the goal of understanding CMS.

KEYWORDS

Cytoplasmic male sterility; gene loss; gene transfer; genome rearrangement; plant mitochondrial genomes; repeated sequences

I. Mitochondria and cytoplasmic male sterility: An overview

Mitochondria are a semi-autonomous and primarily maternally inherited genetic organellar system responsible for producing cellular ATP by oxidative phosphorylation (Gray *et al.*, 1999; Gray, 2012). Land plant mitochondrial genomes (mitogenomes) are notably different from other eukaryotic mitochondria due to their paradoxical mixture of extraordinarily fast and slow rates of evolution. Flowering plant mitogenomes exemplify the former, with substantial variation in genome size and structure even among close relatives (Francis and Fernand, 1977; Alverson *et al.*, 2010; Tang *et al.*, 2015; Chen *et al.*, 2017). They have highly variable intergenetic regions containing diverse repeated sequences (Kitazaki and Kubo, 2010), frequent structural rearrangements (Galtier, 2011), massive genes loss, frequent endogenous and foreign DNA transfer (Bergthorsson *et al.*, 2003; Kubo and Newton, 2008; Hao and Palmer, 2009; Bock, 2010; Liu *et al.*, 2011), and a highly variable RNA editing process (Takenaka *et al.*, 2008). Conversely, plant mitochondrial genes display exceptionally low rates of nucleotide substitution (Wolfe *et al.*, 1987; Palmer *et al.*, 2000; Mower *et al.*, 2007; Galtier, 2011). This contrast between the pace of mitochondrial genomic and genic evolution has led to many questions regarding these disparate patterns of evolution. Among these is the question of how mitochondrial gene and genome evolution influence the interactions of the nuclear genome and the origin of cytoplasmic male sterility (CMS).

CMS is a maternally inherited trait conferred by the mitochondrial genome that results in a failure to produce functional pollen and/or male reproductive organs (Pruitt and Hanson, 1991; Budar and Pelletier, 2001; Chase, 2007; Kubo *et al.*, 2011; Suzuki *et al.*, 2013), except in the presence of restorer-of-fertility genes (Chase, 2007; Cho *et al.*, 2012; Lee *et al.*, 2014; Huang *et al.*, 2015). CMS is also important in specifying gynodioecy in natural populations (Hanson and Bentolila, 2004; Miller and Bruns, 2016), a phylogenetically widespread reproductive strategy in flowering plants. CMS has been detected in more than 150 species (Carlsson *et al.*, 2008), and gynodioecy may occur in as many as 7% of angiosperm species (Ornduff, 1986; Budar and Pelletier, 2001; McCauley and Bailey, 2009). Not only

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does CMS confer a prominent breeding system (second only to hermaphrodism [Budar and Pelletier, 2001]), but it also has led to significant gains in agriculture mediated by heterosis in crop plants and large-scale commercial production of F_1 hybrid seed (Havey, 2004; Chen and Liu, 2014; Bohra *et al.*, 2016). Understanding the mechanisms of CMS, therefore, has broad importance to plant biology and agronomy.

In this review, we describe the composition and characteristics of plant mitogenomes, and the functional interactions and propensity for endogenous gene transfer between plant nuclear and organellar genomes. We review recent advances in understanding several mechanisms that are known to underlie CMS in plants, with a focus on peculiarities specific to CMS-associated genes. Throughout, we emphasize the connection between processes of mitogenome evolution and the role of CMS in plant biology and crop improvement.

II. Characteristics of plant mitochondrial genomes: High variability and complexity conferred by repeated sequences

Plant mitogenomes are notable for both their extraordinary variation in genome size and their remarkable variability in structure and organization. By contrast, vertebrate animal mitogenomes are rather small (~14–20 kb) and highly conserved in both size and structure (Boore, 1999; Lavrov *et al.*, 2016), and plant mitochondrial genomes exhibit substantial variation in both these features (Kitazaki and Kubo, 2010; Galtier, 2011; Mower *et al.*, 2012b), although exceptions exist in nonflowering plants (Liu *et al.*, 2014; Guo *et al.*, 2016). Plant mitochondrial genomes may vary enormously in size even within single plant families; in the Cucurbitaceae, for example, mitochondrial genomes vary over 7-fold in size, from 379 kb in *Citrullus lanatus* (Alverson *et al.*, 2010) to 2,740 kb in *Cucumis melo* (Rodriguez-Moreno *et al.*, 2011). Even more spectacularly, within the single genus *Silene*, mitogenome sizes vary over 40-fold in size, from 253 kb in Silene latifolia (Sloan *et al.*, 2010) to more than 11 Mb in *Silene conica* (Sloan *et al.*, 2010). Analyses of composition reveal that the size variability of these mitogenomes does not reflect differences in the number of functional genes (Clifton *et al.*, 2004), but rather differences in the intergenic space (Cupp and Nielsen, 2014). The factors contributing to this variation are diverse and include variable accumulation of diverse repeated sequences; inclusion of unknown sequences (Palmer *et al.*, 2000; Bergthorsson *et al.*, 2004; Alverson *et al.*, 2010; Rice *et al.*, 2013); variation in intronic size (Laroche *et al.*, 1997; Satoh *et al.*, 2004); and differences in pseudogene fragment number and size (Knoop, 2013).

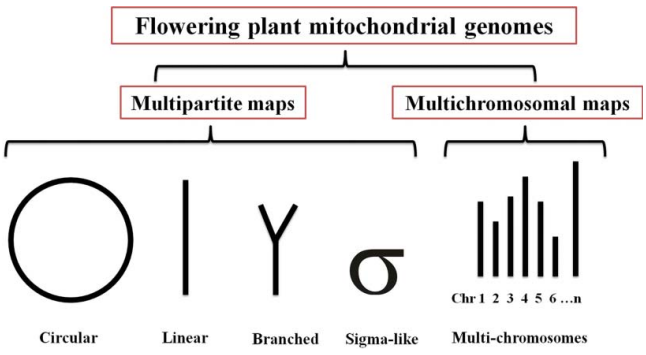

Figure 1. Multipartite and multichromosomal plant mitogenome maps.

In addition to variability in size, the structure of mitogenomes is remarkably variable (Mower *et al.*, 2012b). While mitogenomes typically are depicted as single circular rings (Kitazaki and Kubo, 2010), many other configurations for plant mitochondrial chromosomes have been reported (Figure 1), including diverse linear and circular forms, highly branched and sigma-like morphologies, as well as multichromosomal structures that are capable of substoichiometric co-occurrence. The mitochondrial genomes of some CMS lines in maize (Allen *et al.*, 2007) and rice, for example, have linear configurations (Notsu *et al.*, 2002). Conversely, the mitochondrial genome of garden rocket (*Eruca sativa* Mill.) is multipartite, consisting of six master circles and four smaller subgenomic circles which likely result from repeat-induced genomic reorganization (Wang *et al.*, 2014). A similar configuration has been observed in *Brassica oleracea*, which displays a tripartite structure consisting of a 220 kb master circle that is also split into two subgenomic circles (170 and 50 kb each) via homologous recombination of repeated sequences (Grewe *et al.*, 2014). Observations in the *hau* CMS line of *Brassica* and its maintainer line in *B. juncea* suggest not only a multipartite structure, but also the substoichiometric coexistence of different mitotypes (Heng *et al.*, 2014). Multichromosomal mitochondrial genomes have been identified in four independent angiosperm lineages (Alverson *et al.*, 2011a; Sloan *et al.*, 2012a; Rice *et al.*, 2013; Sanchez-Puerta *et al.*, 2017). These two configurations, i.e., multipartite and multichromosomal maps, are not intuitively different and indeed may be alternative representations of the same genome. The distinction typically relies on the number of chromosomes (Gualberto and Newton, 2017; Sanchez-Puerta *et al.*, 2017). That is, multipartite maps typically contain fewer than three chromosomes that can be assembled into the forms noted in Figure 1 (Gualberto and Newton, 2017), whereas multichromosomal maps contain up to 50–100

linear or circular chromosomes (Alverson *et al.*, 2011a; Sloan *et al.*, 2012a; Rice *et al.*, 2013; Sanchez-Puerta *et al.*, 2017).

The accumulated evidence, therefore, is that plant mitochondrial genomes frequently have a multipartite organization (Kitazaki and Kubo, 2010) associated with complex recombination among repeated sequences (Oldenburg and Bendich, 1996; Backert and Borner, 2000). In general, mitogenomes are arranged in a main ring (i.e., a "master chromosome") that contains a complete set of genes and a number of sub-rings (Alverson *et al.*, 2011a, b). Alternatively, they can be reconstructed configurations produced by frequent recombination among repeated sequences (Lonsdale *et al.*, 1988; Kubo *et al.*, 2000; Handa, 2003; Sugiyama *et al.*, 2005; Marechal and Brisson, 2010).

Repeated sequences are common in plant mitochondrial genomes, with estimates of up to 38% of the mitochondrial genome occupied by repeats of variable size and copy number (Mower *et al.*, 2012b). This number surely is an underestimate, as some of the large mitogenomes, e.g. in *Silene* or the Curcurbitaceae noted above, likely reflect the accumulation and decay of multiple diverse repeated elements. The origin of these repeats is often unclear, as are the mechanisms that underlie the propensity for mitogenomes to acquire repetitive sequences. From the >60 sequenced mitogenomes (Mower *et al.*, 2012b; Gualberto *et al.*, 2014; Liu *et al.*, 2014), it is clear that plant mitogenomes vary widely in repeat content and composition, which, in conjunction with the phylogenetically widespread occurrence of large mitogenomes, lend support to the idea that multiple divergent repeated sequences are acquired independently during evolution (Andre *et al.*, 1992). Consequently, as the presence of repeated sequences is associated with recombination in the mitogenome (Manchekar *et al.*, 2006; Kitazaki and Kubo, 2010; Chen *et al.*, 2017), the high structural variability (Ogihara *et al.*, 2005), complexity, and multipartite organization of plant mtDNA (Abdelnoor *et al.*, 2003) should come as little surprise.

The highly recombinogenic, repetitive nature of plant mitogenomes has been linked to various traits, including CMS (Galtier, 2011), and, intriguingly, the presence of CMS may be associated with the presence of large repeats. CMS is typically conferred via chimeric genes (Section VI.A.1), whose generation has been associated with the presence of large repeats. In Brassica juncea, for example, comparison between the *hau* CMS line and its maintainer line revealed that repeats in the CMS line were typically twice the size as those in the maintainer line (for repeats >100 bp). Furthermore, the presence of three large repeats downstream from the *hau* CMS-associated gene *orf288* has been implicated in the formation of this chimera (Heng *et al.*, 2014). Comparative analysis between the mitogenomes of CMS and male-fertile lines of pepper (*Capsicum annuum* L.) showed that CMS candidate genes *orf507* and *ψatp6-2* were proximal to edges of highly rearranged CMS-specific DNA regions, whose evolution may be the result of nearby intermediate or large-sized repeats (Jo *et al.*, 2014). While recombination in short repeats is rare and has yet to be associated with CMS (Touzet and Meyer, 2014), these repeats may have played other roles in evolution (Andre *et al.*, 1992), leading to other deficiencies such as respiratory impairments (Kitazaki and Kubo, 2010). A final comment is that many nuclear genes, including *Msh1* (Abdelnoor *et al.*, 2003; Shedge *et al.*, 2007; Galtier, 2011), *RecA2* (Shedge *et al.*, 2007), *RecA1/4* (Odahara *et al.*, 2009) and *OSB1* (Zaegel *et al.*, 2006), appear to participate in the regulation of recombination events for different repeated sequences (Lillestol *et al.*, 2009; Cupp and Nielsen, 2014; Gualberto and Newton, 2017), which may represent an additional cytonuclear process important in the origin of CMS.

III. Gene loss and collinearity

While most genes required for mitochondrial metabolism are encoded by the nuclear genome, plant mitochondria commonly contain a suite of approximately 67 essential genes (Kurland and Andersson, 2000) that typically are conserved in both type and number (Kitazaki and Kubo, 2010). These include protein-encoding, rRNA, and tRNA genes, in addition to pseudogenes and ORFs of unknown function, the latter having been implicated in CMS (Satoh *et al.*, 2004; Luo *et al.*, 2013). Conservation and loss of these genes in different plant groups have been extensively studied (Rice *et al.*, 2013; Skippington *et al.*, 2015; Skippington *et al.*, 2017). Plant mitochondrial protein-encoding genes are commonly divided into five categories (participating in five complexes or subunits associated with mitochondrial respiratory metabolism; Figure 2 [Lei *et al.*, 2013]), which typically are conserved among plants, albeit to varying degrees. Genes classified in complex II, for example, have been lost in most higher plants, particularly in monocots, whereas complexes I, III, IV, and V show much greater conservation across land plant species with occasionally loss of *nad* genes (*Viscum scurruloideum*) and *cox2* (legumes) (Palmer *et al.*, 2000; Fujii *et al.*, 2007; Bentolila and Stefanov, 2012; Rice *et al.*, 2013; Skippington *et al.*, 2015; Skippington *et al.*, 2017). Conversely, both the ribosomal subunit and tRNA-encoding genes have experienced a more dynamic pattern of evolution (Figure 2), often displaying progressive loss, and

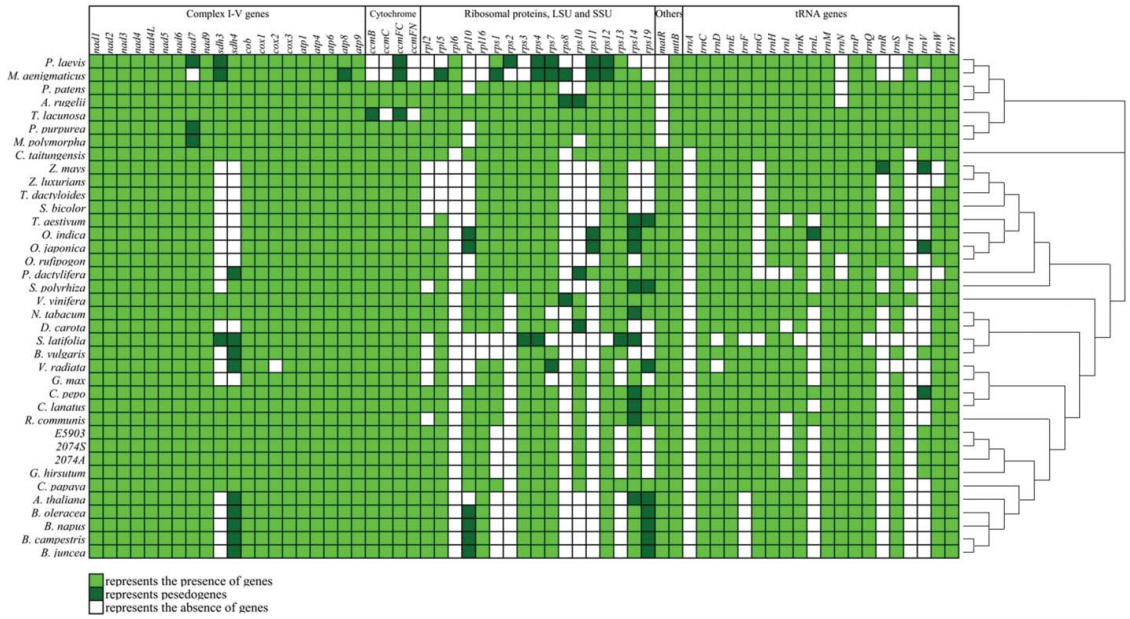

Figure 2. Gene content in sequenced mitogenomes from 38 plant species (2074A, 2074S, and E5903 were two sterile lines and one restoring line associated with cotton, respectively). The genes included encode proteins, rRNAs, and tRNAs. Protein-coding genes are shown in the following order (top to bottom): those associated with complex I-V, cytochrome C synthetase subunits, ribosomal protein large and small subunits, and intron maturase. Boxes in light green, dark green, and white represent intact genes, pseudogenes, and the absence of genes, respectively. The maximum likelihood phylogenetic tree was constructed based on 17 mitochondial genes related to the respiratory chain: *nad1, nad2, nad3, nad4, nad4L, nad5, nad6, nad9, cob, cox1, cox2, cox3, atp1, atp4, atp6, atp*8, and *atp9*.

collectively representing the majority of cases of genic variation among plant mitogenomes (Clifton *et al.*, 2004; Lei *et al.*, 2013). Most gene "losses" are not complete removals but rather reflect functional transfer to the nuclear genome, where they encode products that return to the mitochondria (Palmer *et al.*, 2000; Adams and Palmer, 2003). Other true losses, such as "missing" tRNAs, have been compensated for by native analogs in the nuclear or chloroplast genomes. Namely, nuclear-derived tRNA are expressed and then imported into mitochondria. In contrast, plastid tRNA genes have been transferred into the mitochondrial genome where they are locally expressed (Marechal-Drouard *et al.*, 1990; Schneider, 2011; Liu *et al.*, 2013).

Notwithstanding the many cases of mitochondrial gene loss, gene content is far more conserved than gene order, which varies enormously among angiosperm plants. This variation can be observed even between accessions of the same species (Liu *et al.*, 2013; Tuteja *et al.*, 2013). This frequent recombination common to plant mitogenomes disrupts and reorganizes syntenic blocks, as has been demonstrated in the comparison among *Gossypium* species (Tang *et al.*, 2015; Chen *et al.*, 2017). Notably, some evidence suggests that at least in some cases, natural selection may have played a key role in shaping the evolution of syntenic gene clusters. Specifically, some syntenic clusters are co-transcribed, such as *rrn5-rrn18, rps3-rpl16* and *nad3-rps12* in rice and palm, among others (Nakazono *et al.*, 1995; Fang *et al.*, 2012). While the origin of these syntenic co-transcribed gene clusters is unclear, they appear to be distributed consistently throughout plant taxonomic groups (Liu *et al.*, 2013).

IV. Unidirectional gene transfer and bidirectional functional interactions between chloroplasts and mitochondria

A characteristic of plant mitogenomes is their propensity for becoming a genetic "dumping ground" for sequences from both the nuclear and chloroplast (cp) genomes. Whereas this process is bidirectional between the mitochondrial and nuclear genomes (Knoop *et al.*, 1996; Stupar *et al.*, 2001; Timmis *et al.*, 2004; Lough *et al.*, 2008), sequence transfer from chloroplast to mitochondrial genomes typically is one-way (Hao and Palmer, 2009; Smith, 2011; Tsunewaki, 2011), with two notable exceptions of mitochondrion-to-plastid transfer in *Daucus carota* (Goremykin *et al.*, 2009) and *Asclepias syriaca* (Smith, 2014). Genetic transfer from the chloroplast to the mitochondrial genome is well documented (Oldenburg and Bendich, 1996; Bock, 2010; Smith, 2011), with cpDNA-like sequences detected in many mitogenomes from a variety of species (Alverson *et al.*,

2010; Kitazaki and Kubo, 2010; Rodriguez-Moreno *et al.*, 2011). As an indication of the scale of this process, between 0.1 and 10.3% of mtDNA has an origin tracing back to the chloroplast genome (Kitazaki and Kubo, 2010; Sloan and Wu, 2014); again, this likely underestimates the upper end of the range (Alverson *et al.*, 2010).

Conversely, transfers in the reverse direction, i.e., mitochondria to chloroplasts, are rare. Aside from a few notable exceptions (*Daucus carota, Asclepias syriaca* and *sensu lato*) of horizontal gene transfer into the chloroplast (Mackenzie and Chase, 1990; Goremykin *et al.*, 2009; Lei *et al.*, 2013; Knox, 2014; Smith, 2014), the chloroplast genome is highly conserved among plant species, and is unlikely to accept foreign sequences (Kitazaki and Kubo, 2010). Those infrequent cases of horizontal gene transfer into the chloroplast most commonly are associated with double-strand break repair and interestingly, are more likely to occur if a plastid-to-mitochondria transfer event had occurred previously (Mackenzie and Chase, 1990; Christensen, 2013).

Exogenous sequence uptake into plant mitochondrial is common and ongoing, occurring throughout land plants (Kitazaki and Kubo, 2010; Rodriguez-Moreno, 2011). There is, however, a notable difference in the propensity for chloroplast DNA (e.g. cpDNA-derived tRNA genes) uptake among mitochondria in land plants (Figure 3), with a greater number and longer average length in seed plants. Additionally, while a variety of chloroplast sequences are found in land plant mitogenomes, most functionally transferred genes are tRNAs

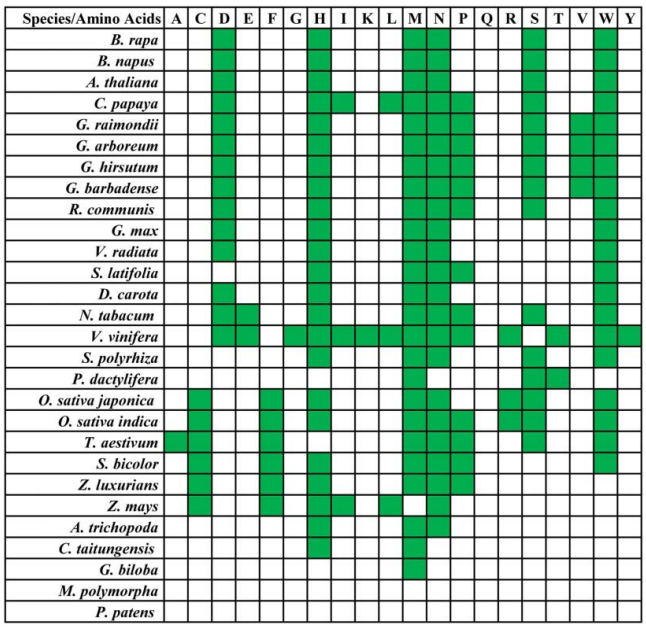

Figure 3. Distribution of chloroplast-derived tRNA genes in land plant mitogenomes (in green).

(Figure 3). Almost half of the donated cpDNA-like sequences are related to tRNAs, although a few are related to genes involved in photosynthesis or other functions (Nakazono *et al.*, 1996; Adams *et al.*, 2002a; Wang *et al.*, 2012; Liu *et al.*, 2013). Many of these are maintained after transfer (Dietrich *et al.*, 1996; Clifton *et al.*, 2004; Sloan *et al.*, 2010). However, some copies become degenerate upon integration and/or over time (Wang *et al.*, 2007), which can lead to the formation of detrimental CMS-introducing ORFs. Perhaps more intriguing is the common conversion of regions of the *atp1*/*atpA* mitochondrial gene copy such that the chloroplast and mitochondrial copies are unusually conserved (Hao and Palmer, 2009). Moreover, some chloroplast-derived sequences have been shown to maintain syntenic relationships with specific mitochondrial sequences, even among species separated by millions of years of divergence (Liu *et al.*, 2013).

Unlike the pattern observed with the chloroplast, nuclear-mitochondrial transfers are bidirectional (Francis and Fernand, 1977; Bock, 2010) and can contribute a significant amount of DNA to either genome. Nuclear-derived sequences have been found in the mitogenomes of multiple species (Unseld *et al.*, 1997; Alverson *et al.*, 2010; Rodriguez-Moreno *et al.*, 2011), comprising nearly half of the maize mitogenome (Goremykin *et al.*, 2012) and typically falling between 0.1 and 38.6% (Kubo and Newton, 2008; Rodriguez-Moreno *et al.*, 2011; Goremykin *et al.*, 2012). Reciprocally, there exist numerous examples of mitochondrial sequences becoming incorporated in the nuclear genome, often as nonfunctional NUMTs (i.e. NUclear MiTochondrial DNAs). These range in size from short transfers of only ~20 kb nucleotides (Liu *et al.*, 2014) to hundreds of kilobases of mtDNA in complex arrangements (Lin *et al.*, 1999; Stupar *et al.*, 2001; Bergthorsson *et al.*, 2003; Yu *et al.*, 2003; Lough *et al.*, 2008). The origin and fate of transferred sequences have been facilitated to be clarified by the increased availability of genomic sequences (Adams *et al.*, 2000, 2002b; Noutsos *et al.*, 2005; Mower *et al.*, 2012a; Michalovova *et al.*, 2013).

In addition to nonfunctional transfers, the nuclear genome can also uptake genic sequences from the mitochondria (Adams *et al.*, 2002a; Adams and Palmer, 2003; Mower *et al.*, 2012a), subsequently acquiring both the regulatory factors (de Longevialle *et al.*, 2007) and targeting information necessary for successful transfer of the protein products back to the mitochondria (Peeters and Small, 2001; Liu *et al.*, 2009). This is perhaps not entirely surprising in that communication between the mitochondrial and nuclear genomes is necessary for successful mitochondrial function (Poyton and McEwen, 1996; Cannino

et al., 2007; Jacoby *et al.*, 2012; Arenas-M *et al.*, 2014; Braun *et al.*, 2014), as well as regulation of some nuclear genes (Yuan and Yang, 1999), such as those involved in pathogen response (Colombatti *et al.*, 2014). Indeed, of the more than 2000 proteins contained within angiosperm mitochondria, typically fewer than 41 proteins are encoded by the mitogenome itself (Millar *et al.*, 2005).

V. Mechanisms of cytoplasmic male sterility (CMS)

CMS is a maternally conferred reproductive trait that relies on the expression of CMS-inducing mitochondrial sequences and the presence (or absence) of nuclear-based fertility restoring sequences (Chen and Liu, 2014). Factors implicated in the evolution of CMS include wide interspecific or inter-generic hybridization (Gobron *et al.*, 2013), cell fusion (Yamagishi and Bhat, 2014), and intron cleavage (Jin *et al.*, 2013). At the molecular level, the development of CMS can be broadly binned into the following three main categories: (1) mtDNA recombination and interactions between mitochondrial and nuclear genomes; (2) aberrant RNA editing; and (3) accumulation of toxic protein products.

A. Three routes to CMS

1. mtDNA recombination and cytonuclear interaction

Both the rampant recombination in plant mitogenomes and the propensity for intergenomic sequence transfer are involved in CMS determination at the genome level, with the former acting to induce CMS and the latter to resolve it. As described above, mitogenome recombinations generate novel chimeric sequences. Many examples of CMS stem from these consequences of recombination (Sloan *et al.*, 2012b; Chen and Liu, 2014; Yamagishi and Bhat, 2014; Charlesworth, 2017; Tang *et al.*, 2017), and include chimeric gene fusions (Rathburn and Hedgcoth, 1991; Tuteja *et al.*, 2013; Wang *et al.*, 2013b; Szklarczyk *et al.*, 2014; Tang *et al.*, 2017), partial/orphan ORFs (Shearman *et al.*, 2014), and disruptions in gene orientation/promoter association (Horn *et al.*, 2014). Often, these chimeric CMS genes exhibit co-transcription with upstream or downstream functional genes, such as T-*urf13* in CMS-T maize (Wise *et al.*, 1987; Kennell and Pring, 1989), *orf352* in RT102-CMS rice (Okazaki *et al.*, 2013), and *orf355* and *orf77* in CMS-S maize (Wen and Chase, 1999; Gallagher *et al.*, 2002). CMS genes typically affect the mitochondrial electron transfer chain pathways, and are commonly classified into four categories according to the components they affect: [1] complex I (NADH dehydrogenase); [2] complex IV (cytochrome oxidase); [3] complex V (F_0F_1 ATP synthase); and [4] "other" (Horn *et al.*, 2014; Wesołowski *et al.*, 2015).

If the development of CMS-inducing genes in the mitochondria blocks successful reproduction, compensation for these defects is required for fertility. Indeed, restorer-of-fertility genes (RFs) have been identified in and/or suggested for many CMS systems (Forde *et al.*, 1978; Bonhomme *et al.*, 1991; Rathburn and Hedgcoth, 1991; Ducos *et al.*, 2001; Liu *et al.*, 2007; Luo *et al.*, 2013; Wang *et al.*, 2013a; Table 1 in Hu *et al.*, 2014; Table 1 in Chen and Liu, 2014; Kim *et al.*, 2015). These are encoded not by the mitochondria, but by sequences in the nuclear genome. That is, sterility is reversed through synergistic cytonuclear interactions and antero/retrograde signaling between the mitochondrial and nuclear genomes (Rhoads and Subbaiah, 2007; Chen and Liu, 2014; Kitazaki *et al.*, 2015; Liu *et al.*, 2016). The exact nature of many of these RF loci, however, remains unknown. In a comprehensive review regarding the mechanisms underlying CMS, Chen and Liu (2014) tabulated a list of known CMS + RF systems from diverse species, including maize, sunflower, and radish (Chen and Liu, 2014) and their mode of action, if known. Remarkably, many of the properties of the RF loci remain unknown. However, the coding capacity for those that are known (or can be predicted) are quite diverse, from an aldehyde dehydrogenase in maize (the first isolated plant restorer gene, Cui *et al.*, 1996; Liu *et al.*, 2001) to a putative peptidase in sugar beet (Matsuhira *et al.*, 2012) to a suite of PPR proteins in diverse species (Brown *et al.*, 2003; Kazama and Toriyama, 2003; Koizuka *et al.*, 2003; Akagi *et al.*, 2004; Komori *et al.*, 2004; Klein *et al.*, 2005; Wang *et al.*, 2006; Uyttewaal *et al.*, 2008; Jordan *et al.*, 2010; Hu *et al.*, 2012; Wang *et al.*, 2013c; Kitazaki *et al.*, 2015; Liu *et al.*, 2016).

The modes of action for CMS-related mitochondrial genes appear equally as diverse. In *Brassica napus*, CMS-related *orf224/atp6* was found to downregulate pollen development by causing an energy deficiency (An *et al.*, 2014). Whereas CMS in Chinese cabbage has been associated with retrograde signaling (i.e., signals from the plastid or mitochondrion that control nuclear gene expression) from the mitochondrion that interferes with nuclear gene expression in a suite of pathways, including auxin response, ATP synthesis, and more (Dong *et al.*, 2013). Maladaptive retrograde signaling has also been implicated in mitochondrial interference with the rice nuclear gene *COX11*, resulting in the premature programmed cell death of tapetal cells and subsequent pollen abortion (Luo *et al.*, 2013). Still, other species have the features and function of cytotoxic proteins (Dewey

et al., 1987; Korth *et al.*, 1991; Levings, 1993; Korth and Levings, 1993; Nakai *et al.*, 1995; Duroc *et al.*, 2005; Wang *et al.*, 2006; Jing *et al.*, 2012).

Broad characterization of the mechanisms that cause CMS has led to the following four accepted models: (1) the energy deficiency model; (2) the retrograde regulation module; (3) the aberrant programmed cell death model; and (4) the cytotoxicity model. However, as is the case with rice *COX11* and other CMS systems, the mode of action may affect more than one category. An additional interesting dimension is that while the expression of CMS genes does not appear to be restricted to the male reproductive tissues in many species (Warmke and Lee, 1978; Abad *et al.*, 1995; Yamamoto *et al.*, 2008; Chen and Liu, 2014), accumulation of CMS-related proteins can be highly spatiotemporally specific to induce CMS (Abad *et al.*, 1995; Wang *et al.*, 2006; Luo *et al.*, 2013).

2. Regulation of CMS transcripts via RNA editing

Post-transcriptional RNA editing of mitochondrial genes is both ubiquitous and important for regulation (Marchfelder and Binder, 2004; Takenaka *et al.*, 2008; Wang *et al.*, 2009; Grewe *et al.*, 2014). Typically, RNA editing of mitochondrial transcripts in flowering plants occurs in coding regions of mitochondrial transcripts (Hanson *et al.*, 1996) to convert specific cytosine residues to uracil (C → U) (Yi *et al.*, 2004; Bentolila *et al.*, 2008; Suzuki *et al.*, 2013; Szklarczyk *et al.*, 2014; Takenaka *et al.*, 2014). Defects in proper RNA editing have been associated with truncated or repressed transcripts, ultimately resulting in plant or cell death (Amuthan *et al.*, 2001). In the case of CMS, RF genes modulate specific RNA editing through cleavage and/or degradation of the CMS products, thereby restoring fertility (Chen and Liu, 2014; Yan *et al.*, 2015). Regulation of CMS products by RF-mediated, RNA editing occurs diverse species, from sorghum (Tang *et al.*, 1999) to *Brassica* (Menassa *et al.*, 1999) to rice (Wang *et al.*, 2006), and reduction in RNA editing of CMS genes has been associated with sterility (Suzuki *et al.*, 2013). Maize CMS-associated *orf77* shows significant reduction in editing in sterile lines (Gallagher *et al.*, 2002), as does CMS-associated *atp6* in *Sorghum bicolor* (Howad and Kempken, 1997) and *atp9* in rice and soybean (Wei *et al.*, 2008). The number of RNA editing sites can vary among species, e.g., an average 43 different editable sites among mitochondrial protein-coding regions of *Arabidopsis thaliana* (Giege and Brennicke, 1999), *Brassica napus* (Handa, 2003), and *Oryza sativa* (Notsu *et al.*, 2002), as well as among tissues, ecotypes, or genes (Bentolila *et al.*, 2008). This link between RNA editing and CMS is not ubiquitous for all plants (Horn *et al.*, 2014). Finally, recent degradome sequencing implicates a possible role for microRNAs in the regulatory network of *Brassica juncea* and *Raphanus sativus* CMS (Yang *et al.*, 2013; Zhang *et al.*, 2016).

3. Specific protein products

In all known cases, the protein products of CMS genes are the likely agents of CMS, not the transcripts themselves that. Most CMS-associated proteins possess transmembrane configurations capable of disrupting the mitochondrial membrane structure and/or altering the permeability and potential of mitochondrial membrane (Li *et al.*, 2014). These proteins can directly interfere with energy production (Jing *et al.*, 2012; Wang *et al.*, 2013c; Wu *et al.*, 2013), induce the release of cytochrome C via accumulation of unusually large numbers of reactive oxygen species (ROS) (Yan *et al.*, 2014), and stimulate premature programmed cell death in male reproductive tissues (Luo *et al.*, 2013; Horn *et al.*, 2014). Several CMS proteins have demonstrated toxicity, such as URF13 in CMS-T maize (Korth *et al.*, 1991), ORFH79 in HL-CMS rice (Hu *et al.*, 2013), *Orf507* in CMS pepper (Li *et al.*, 2013), and ROS homeostasis associated protein in cotton (Yang *et al.*, 2014). Restoration of fertility can occur at the translational or post-translational level. That is, in many CMS systems, RF genes do not affect accumulation of the CMS transcript; rather, restored lines are characterized by a marked decrease in toxic CMS protein accumulation (Chen and Liu, 2014). Reduced protein accumulation (without similar transcript reduction) has been observed in maize (Dewey *et al.*, 1991), common bean (Sarria *et al.*, 1998), *Brassica* (Landgren *et al.*, 1996), radish (Uyttewaal *et al.*, 2008), and rice (Itabashi *et al.*, 2011), among others. Many of these suggest that restoration of fertility occurs via reduction in the production of toxic proteins; however, in at least one maize CMS system, there is evidence that fertility is restored via the degradation of toxic products (versus proteins; Liu *et al.*, 2001).

VI. Conclusions

Mitochondria are the primary source of cellular energy, providing the necessary means for growth, development, and reproduction. These highly conserved functions render the slow evolutionary pace of plant mitochdondrial genes understandable. However, the rapidity with which plant mitogenomes evolve is far more puzzling, given both the potential and observed consequences of this lability, including massive alterations in genome size, organization, and composition. The consequences of and adaptation to mitochondrial gene loss (transfer to the nucleus) and genomic recombination are particularly interesting in that both appear to require cooperation from the nucleus to ensure viability. The tolerance for

recombination, and the resulting consequences, while perhaps surprising for such an essential cellular component, relies largely on a co-evolutionary dynamic among the nucleus and its extra-nuclear genomes.

CMS is a prime example of recombination-induced mitochondrial dysfunction that requires nuclear input for resolution (Hanson and Bentolila, 2004; Pelletier and Budar, 2007). Novel and chimeric mitochondrial sequences are a frequent result of this recombination (Wise *et al.*, 1987; Kennell and Pring, 1989; Wen and Chase, 1999; Gallagher *et al.*, 2002; Okazaki *et al.*, 2013; Yamagishi and Bhat, 2014; Tang *et al.*, 2017), in which recombination sometimes leads to the creation of transcripts that interfere with normal male gametophyte development (Kitazaki and Kubo, 2010) via the generation of toxic and/or disruptive transmembrane proteins (Korth *et al.*, 1991; Kim *et al.*, 2007; Wan *et al.*, 2007; Zhang *et al.*, 2007; Yang *et al.*, 2009; Gulyas *et al.*, 2010; Jing *et al.*, 2012; Flores-Renteria *et al.*, 2013; Ji *et al.*, 2013; Luo *et al.*, 2013; Okazaki *et al.*, 2013; Park *et al.*, 2013; Hu *et al.*, 2014). Surprisingly, such genes are not only abundant in many fertile plants, such as *Arabidopsis thaliana* (Marienfeld *et al.*, 1997; Unseld *et al.*, 1997), *Beta vulgaris* (Kubo *et al.*, 2000), *Oryza sativa* (Notsu *et al.*, 2002), *Brassica napus* (Handa, 2003), *Zea mays* (Clifton *et al.*, 2004), *Triticum aestivum* (Ogihara *et al.*, 2005), and *Nicotiana tabacum* (Sugiyama *et al.*, 2005), but are also constitutively expressed. Research into this phenomenon has revealed much about the distribution and occurrence of CMS, the tissue-specificity of the phenotype (male gametophytic tissues only) (Jing *et al.*, 2012; Hu *et al.*, 2014), the modes of action behind CMS, and the cytonuclear cooperation that suppresses the phenotype (Carlsson *et al.*, 2008). As more genomes (both nuclear and mitochondrial) and other "-omic" data become available (Du *et al.*, 2016; Jacoby *et al.*, 2016; Wang *et al.*, 2016), the potential for increasing our understanding and manipulating this vitally important phenomenon will be enhanced.

Acknowledgments

The authors thank Daniel B. Sloan (Colorado State University), Yingguo Zhu and Shaoqing Li (Wuhan University), Xuequn Liu (South-central University for Nationalities), and Shu-Miaw Chao (Biodiversity Research Center of Academia Sinica, Taipei, China) for their many valuable comments and suggestions. They are also grateful to anonymous reviewers for their helpful comments.

Funding

This work was supported by the National Key R & D Program for Crop Breeding (2016YFD0101407).

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