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Molecular Genetics of Mitochondrial Respiratory/ATP-Related Genes in Relation to Cytoplasmic Male-Sterility of Higher Plants

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ABSTRACT

With the sequencing of the entire mitochondrial genome for some species, including *Arabidopsis thaliana*, *Brassica napus*, *Beta vulgaris*, *Marchantia polymorpha*, *Oryza sativa*, and *Zea mays* it is promising to explore the molecular genetics of mitochondrial respiratory-related genes in relation to some special traits with an emphasis on cytoplasmic male-sterility unique to plant mitochondria. Mitochondrial genomes encode only partial genetic information required for their biogenesis and function, however the vast majority is nuclear-derived, which is encoded by the nucleus and imported into mitochondria through the transported proteins. Consequently, most mitochondrial genetic and biochemical features displayed in plant mitochondria arise from the context of nuclear-mitochondrial co-evolution. Cytoplasmic male sterility (CMS), one useful trait for heterosis in agricultural production, is considered to be the result of the interactions between the mitochondrion and the nucleus in which the former exhibits the role of a tuning fork in nuclear gene expression that induces abnormal reproductive development. Likewise, expression of some mitochondrial genes is also regulated by nuclear genes in which the expression of some CMS-associated genes is influenced by nuclear restorer lines. In this review, we attempt to address the molecular genetics of mitochondrial respiratory/ATP-related genes concomitant with the occurrence of CMS. Furthermore, how the mitochondrion and nucleus interact on a molecular level to influence gene expression and function are also discussed in detail.

Keywords: homeotic gene; interactions of mitochondria-nucleus; mitochondria; mitochondrial inhibitor; transcriptional factor

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INTRODUCTION

Mitochondria are mainly responsible for the essential energy (ATP) for cell life in higher plants. Plant mitochondrial genomes encode only partial genetic information required for their biogenesis and function with the vast majority being nuclear-derived, which is encoded by the nucleus and imported into mitochondria through the transported proteins (Unseld *et al*. 1997). Generally, mutations in mitochondrial genes might induce severe defects in respiration and be lethal. Another kind of mitochondrial gene mutant, chimeric plants, also containing wild-type mitochondria (Karpova *et al*. 2002 and refs therein), and which usually lead to cytoplasmic male sterility (CMS), could be the right system to study mitochondrial mutants.

CMS, one selective approach for the production of F_1 hybrids with essential commercial value, had been descrybed in more than 150 plant species (Laser and Lersten 1972; Kaul 1988), which represented maternally inherited traits of failure to produce functional pollen. It was firstly documented that mitochondrial genes contributed to CMS in terms of their molecular aspect in maize, in which one mitochondrial open reading frame (*orf*), *urf-13*, was identified from maize (Dewey *et al*. 1986, 1987). Consequently, more and more mitochondrial *orfs* involved in CMS were reported in different types of CMS, which exhibited how frequently these mitochondrial rearrangements occurred. In many cases, such *orfs* often originated from mitochondrial genome rearrangements composed of fragments derived from other mitochondrial respiratory-related genes. Alternatively, such rearrangements usually altered the expressions of common genes of mitochondrial respiratory/ATP synthesis complex because of their locations at the flanking region and co-transcription with the above genes. Indeed, the action of mitochondria probably triggering CMS had been reviewed in detail in many species, and more importantly, some powerful experimental evidence had confirmed that mitochondrial factors are likely to play a crucial role in pollen or microspore development (Schnable *et al*. 1998; Budar *et al*. 2001; Hanson *et al*. 2004).

In CMS plants, normal pollen development is halted at a very early or late development stage according to different

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Table1 Mitochondrial genes/sequences involved in cytoplasmic male sterility.

Plant species	ORF	Mitochondrial genes/ gene fragment involved CMS	References
Common bean	*pvs-orf239*	*atp1*, 3′-regions of *cob*, *orf239*	Mackenzie and Chase 1990
Brassica juncea	*orf220*	*atpA*, *nad2*	Zhang *et al.* 2003; Yang *et al.* 2005
Brassica nap	*orf222*	*atp8*, *nad5c*, *orf139*	L'Homme *et al.* 1997
Brassica pol	*orf224*	*atp6*, *rps3*	Singh and Brown 1991; Handa *et al.* 1995
Ogura radish	*orf138*		Bonhomme *et al.* 1992; Krishnasamy *et al.* 1993
Petunia	*pcf*	*atp9*, *cox* II, *urf*, *orf143*, *rps12*, *nad3*	Young and Hanson 1987; Hanson *et al.* 1999
Rice	*orf79*	*atp6*, *cox* I	Akagi *et al.* 1994; Wang *et al.* 2006
Sorghum bicolor	*orf107*	*atp9*	Tang *et al.* 1996
Sunflower	*orf522*	*atpA*, *atp8*	Kohler *et al.* 1991; Moneger *et al.* 1994; Sabar *et al.* 2003
T-maize	*urf-13*	*rrn26*, *atp4*, *tRNA*	Dewey *et al.* 1986

CMS systems (Hanson *et al.* 2004). However, the detailed molecular mechanism of pollen or microspore development has to date not yet been confirmed in CMS systems. In other words, the molecular mechanism of the downstream processes triggering CMS by cytoplasmic factors in CMS systems have been poorly understood. How and in which pathway do mitochondrial factors directly or indirectly alter reproductive development through the interactions of mitochondria and the nucleus?

In this review, we firstly describe all kinds of CMS phenotypes and some mitochondiral factors involved in CMS. Of particular interest, we hypothesize here the probable pathway for the mitochondrial-nuclear interaction inducing CMS or other abnormal reproductive development according to limited experimental evidence.

CMS PHENOTYPES

In most cases, the CMS systems were developed by intra-specific, inter-specific or inter-generic crosses in which alien cytoplasm expressed exhibited alloplasmic cytoplasm (with alien cytoplasm from other species or genera). Major research considered that the alloplasmic CMS usually affected reproductive development but not other developmental events, however, certain experimental evidence reported that root development was also impacted by CMS of *Brassica napus* with *Arabidopsis* cytoplasm, which exhibited reduced shoot dry weight and small leaves at an early stage (Leino *et al.* 2003).

CMS-associated abnormalities might occur at different stages during reproductive development. In some CMS types, such abnormal development is involved in late anther development or pollen maturation, in which the defect appears during the period of meiosis of pollen mother cells resulting in sporophytic or gametophytic CMS types in *Zea mays* (Kamps *et al.* 1996; Kempken and Pring 1999). In this type of CMS, the common flower structure (four whorl floral organ architecture, namely, sepal, petal, stamen and carpel) was not altered. Striking alterations in floral morphology were observed in another type of CMS, in which early steps of reproductive development were affected. This type of CMS exhibited homeotic transformations of degenerated stamens to pinnate, petaloidy, silk-like and carpelloidy floral structures in tobacco (Kofer *et al.* 1991; Zubko *et al.* 2001), wheat (Murai *et al.* 2002), carrot (Linke *et al.* 2003) and mustard (Yang *et al.* 2005). In addition, other types of CMS exhibited degeneration of tapetal cells in sunflower (Smart *et al.* 1994; Balk and Leaver 2001) and unrolled filaments with undehisced anthers in carrot (Struckmeyer and Simon 1986).

MITOCHONDRIAL GENES (ORFS) IN RELATION TO CMS

Since the first case of mitochondrial CMS-associated *orf*, *urf13*, was identified from T-maize (Dewey *et al.* 1986, 1987), mitochondria were focused during the isolation of CMS-associated genes or sequences through comparative research. In many cases, CMS-associated genes or sequences were caused by rearrangements of mitochondrial genomes resulting in the birth of new *orfs* composed of fragments of other mitochondrial respiratory-related genes or non-coding sequences (Schnable and Wise 1998; Kempken and Pring 1999; Hanson and Bentolila 2004). Usually, such chimeric *orfs* were located at the flanking end of mitochondrial respiratory/ATP synthesis-related genes and co-transcribed with these genes. Consequently, the expression of mitochondrial common respiratory/ATP synthesis-related genes were also alternatively decreased in the CMS system. Up to date, numerous mitochondrial rearrangement regions associated with the CMS phenotype have been identified, which indicates the striking manner and frequency of events involved in mitochondrial respiratory/ATP synthesis-related gene regions. Most rearrangements on mitochondrial loci focused on subunit genes of ATP synthesis such as ATP synthesis subunit 4, 6, 8 and 9 genes in CMS-associated loci (Schnable and Wise 1998; Hanson and Bentolila 2004). Still, some subunit genes of the mitochondrial respiratory complex were also observed to be associated with CMS in some CMS species. Examples of mitochondrial *orfs* and mitochondrial respiratory/ATP synthesis-related genes involved in CMS are listed in **Table 1**.

CMS can also be caused at the post-transcriptional level. Cell type-specific loss of *atp6* RNA editing was distinctively present in CMS *Sorghum bicolor* and recovered by the restored gene (Howad *et al.* 1997), and the *atp9* gene was found to be partially edited in anthers of CMS wheat (Kurel *et al.* 1997). Three silent RNA editing sites were reported for mitochondrial *nad3* transcripts in the CMS line of carrot (Rurek 2001) and partial editing for mitochondrial *atp6* and *cox*II genes in rice (Yi *et al.* 2002). RNA editing truncated a chimeric open reading frame (*orf77*) associated with S male-sterility in maize (Gallagher *et al.* 2002). When RNA editing (as a crucial post-transcriptional step for RNA processing in higher plant mitochondria) was specifically altered in some types of CMS, several attempts were made to correlate RNA editing with the occurrence of CMS.

Unfortunately, common strategies to discover CMS-associated mitochondrial factors through comparative research have not been absolutely powerful. Sometimes, the differences between two cytoplasms might arise from evolutionary divergence of different mitochondrial genomes in alloplasmic cytoplasm. Likewise, it should be emphasized that some chimeric mitochondrial *orfs* that had been isolated clearly did not exhibit CMS in *Arabidopsis* (Marienfeld *et al.* 1997). Usually, there are two traditional ways to prove the relationship between specific mitochondrial genes and CMS. One approach is to study the expression of such genes under the control of the restored gene to compare their characterizations in CMS, maintainer fertile and restored lines. Another approach is to directly validate their functions by transgenic engineering, of which mitochondria targeted expression of specific *orfs* exhibited sterility in tobacco expressed *T-urf13* (Chaumont *et al.* 1995), petunia and tobacco expressed *urfs* (Wintz *et al.* 1995) and common bean expres-sed *orf239* (He *et al.* 1996); anti-sense expression of mito-chondrial respiratory complex genes also led to partial or complete pollen sterility in tobacco (Kitashiba *et al.* 1999) and sugar beet (Yui *et al.* 2003). Furthermore, expression of an unedited mitochondrial gene in a fertile line showed that they were sterile in *Arabidopsis* (Gomez-Casati *et al.* 2002), although plant mitochondria could not be easily genetically manipulated.

NUCLEAR-REGULATED EXPRESSION OF MITOCHONDRIAL GENES

Nuclear-regulated expression of mitochondrial genes has been well studied in terms of nuclear restorer genes (nuclear genes with the ability to suppress the CMS phenotype and restore the production of pollen) in the fertile restored line. The majority of nuclear restorer genes operated at the post-transcriptional level, such as RNA editing, processing, and polyadenylation, besides acting by controlling copy number at the DNA level (Janska *et al.* 1998), post-translational modification of CMS-associated proteins (Sarria *et al.* 1998) and compensation of mitochondrial dysfunction at the metabolic level (Liu *et al.* 2001). Some experimental evidence indicated a reduced transcript level for CMS-associated genes (Geddy *et al.* 2005), altered processing for mitochondrial CMS-associated *orfs* (Tang *et al.* 1996; Wise *et al.* 1996; Menassa *et al.* 1999), and tissue-specific polyadenylation of CMS-associated transcripts (Gagliardi and Leaver 1999) under the control of restored genes.

Restored genes have already been identified from petunia (Bentolila *et al.* 2002), rice (Kazama and Toriyama 2003; Akagi *et al.* 2004; Komori *et al.* 2004; Wang *et al.* 2006), maize (Liu *et al.* 2001) and radish (Brown *et al.* 2003; Desloire *et al.* 2003; Koizuka *et al.* 2003). Most of them encoded mitochondrial targeted proteins with pentatricopeptide repeat (PPR) motifs (**Table 2**). PPR proteins constitute a large family, more than 400 members in plants, of which about 60% were predicted to be targeted in mitochondria and involved in post-transcriptional processes (Lurin *et al.* 2004). PPR proteins had been suggested to function as sequence-specific adaptors for a variety of other RNA-associated proteins (Lurin *et al.* 2004), which were primarily and definitively supported by some experimental evidence (Kotera *et al.* 2005; Schmitz-Linneweber *et al.* 2005; Wang *et al.* 2006). Hence, PPR proteins were considered as probable candidates for molecules of nuclear-mitochondrial interactions with essential players in CMS systems.

MITOCHONDRIAL TUNING FORK NUCLEAR TRANSCRIPTIONAL FACTOR AND GENES INVOLVED IN PROGRAMMED CELL DEATH

Until now, there has been no evidence supporting the idea that mitochondrial genes are directly involved in floral organ development, microsporogenesis, or other reproductive development. We thought that all types of abnormal phenotypes in CMS should originate from alterations in the expression of nuclear gene signals regulated by mitochondria, which would lead indirectly, but specifically to male sterility. Indeed, two groups of nuclear genes had been reported to be potential target genes: genes involved in programmed cell death (PCD) and transcriptional factor genes needed for development of floral organs as well as pollen.

In tapetal cell degeneration inducing the male sterile type of CMS, PCD of tapetal cells subsequently extended to other tissues of anthers and were shown to be activated by the partial release of cytochrome c from the mitochondria into the above cells (Balk and Leaver 2001). In higher plants, the role of mitochondria involved in PCD has been reviewed (Lam *et al.* 2001; Vacca *et al.* 2004), although unlike the well documented investigations in animals (Goldenthal and Marin-Garcia 2004; Orrenius 2004). Although no definitive evidence supported the casual relationship between PCD and CMS formation, it still offered us a possible approach to investigate how and in which pathway nuclear-mitochondrial interactions induced CMS.

Research on the homeotic-type of CMS clearly demonstrated the probable pathway for the effect of mitochondria on the expression of specific nuclear homeotic genes for floral organ development. In higher plants, floral organ development has been intensively researched in dicotyledonary plants, especially in *Arabidopsis* and *Antirrhinum*, which are mainly controlled by the homeotic genes (Theißen and Saedler 1999; Theißen 2001). One classical genetic model, the ABC model, in developmental biology, can explain and predict flower organ families based on three classes of nuclear homeotic genes, termed A, B, and C (Davies and Schwarz-Sommer 1994; Ma 1994; Weigel and Meyerowitz 1994; extensively reviewed in Teixeira da Silva 2006). Any alterations of transcription or mutation in these genes could lead to global variations in four whorl structures of a flower, of which a certain type of flower organ would be replaced by another (Coen and Meyerowitz 1991; Mandel *et al.* 1992). Interestingly, such dramatic variations in flower organ were observed in alloplasmic cytoplasmic male sterile (CMS) tobacco (Kofer *et al.* 1991), carrot (Linke *et al.* 1999), wheat (Murai and Tsunewaki 1993) and mustard (Yang *et al.* 2005), which, in most cases, exhibited a complete conversion of stamens into other floral organs. In recent research, nuclear MADS-box transcriptional factor (TF) genes, *APETALA3*-, *GLOBOSA*- and *DEFICIENS*-like genes, were found to be transcriptionally down-regulated in CMS carpelloid tobacco flowers (Zubko *et al.* 2001), CMS pistillody carrot (Linke *et al.* 2003), *Brassica napus* (Teixeira *et al.* 2005) and wheat (Murai *et al.* 2002; Hama *et al.* 2004). Likewise, another TF gene, *SUPERMAN* (*SUP*), also seemed to be involved in the generation of homeotic CMS flowers in tobacco, of which homeotic transformations could be partially restored by ectopic expression of the *SUP* gene (Bereterbide *et al.* 2002).

Insightful studies of microsporogensis in *Arabidopsis* introduced molecular genetics into the area of developmental biology (Schiefthaler *et al.* 1999; Yang *et al.* 1999; Ito *et al.* 2004). Of the homeotic genes, *AGAMOUS* (*AG*) triggered reproductive development, which was initially expressed throughout these primordia and involved a series of gene expressions (Wellmer *et al.* 2004). Recent research about putative target genes of *AG* showed that the homeotic protein AG controlled microsporogenesis by regulation of the *SPOROCYTELESS* (*SPL*) gene in Arabidopsis (Ito *et al.* 2004). The *SPL* (also known as *NOZZLE*, *NZZ*) gene, encoding a novel nuclear protein related to MADS-box transcription factor, was required to promote the differentiation of the primary sporogenous cells and cells of the anther wall in *Arabidopsis* (Schiefthaler *et al.* 1999; Yang *et al.* 1999). In cytoplasmic male sterile plants, pollen development was halted at a very early or late developmental stage depending on the CMS system (Hanson *et al.* 2004). However, the detailed molecular mechanism of pollen or microspore development has to date not yet been confirmed in CMS systems. In our present studies about CMS *Brassica juncea* (failure of microsporogenesis type of CMS), we firstly showed the absence of expression of the *SPL* gene during microsporogensis. In addition, we found that such TF genes were also down-regulated when we artificially suppressed the mitochondrial function (submitted for publication). All the above mitochondrial down-regulated nuclear TF genes in CMS abnormal reproductive development allowed us to hypothesize one new pathway to find the exact molecular mechanism of this type of CMS: MADS-like transcriptional factor genes subjected to mitochondrial regulation induce cytoplasmic male sterility in this type of CMS.

Table 2 Examples of identified restorer genes in cytoplasmic male-sterile system.

Restorer gene	Encoded protein/function	CMS system	References
Rf	PPR protein/post-transcriptional regulation	*pcf* petunia	Bentolila *et al.* 2002
Rf-1	PPR protein/post-transcriptional regulation	*boro* rice	Akagi *et al.* 2004; Komori *et al.* 2004
Rf1A, *Rf1B*	PPR protein/post-transcriptional regulation	*boro* II rice	Wang *et al.* 2006
Rf2	Aldehyde dehydrogenase	T-CMS maize	Liu *et al.* 2001
Rfo, RFk1	PPR protein/post-transcriptional regulation	*ogura*, *kosena* radish	Brown *et al.* 2003; Koizuka *et al.* 2003

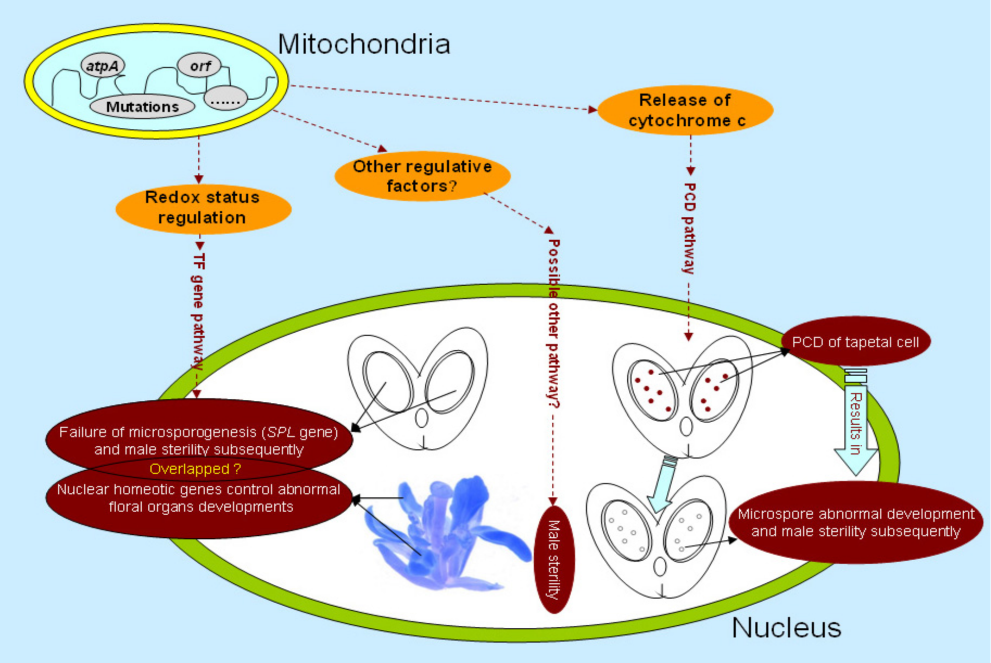

Fig. 1 A hypothesized pathway for mitochondrial-nuclear interactions inducing cytoplasmic male sterility in higher plants.

SIGNALS INVOLVED IN NUCLEAR-MITOCHONDRIA COMMUNICATIONS

Nuclear contributions to mitochondrial gene expression have long been studied and PPR proteins have been validated as playing a key role of restoration of fertility as discussed above (e.g. Binder *et al.* 1996; Mackenzie and McIntosh 1999). However, to date, mitochondrial effects on the nucleus (called retrograde regulation, Liao and Butow 1993) have not been well documented in higher plants, though they have been well described in yeast and mammals (Poyton and McEwen 1996; Burke *et al.* 1997; Butow and Avadhani 2004; Kelly and Searpulla 2004). It was unlikely that the production of mitochondrial genes could directly affect the expression of nuclear genes because of the undiscovered transport proteins and RNAs from mitochondria to cytoplasm thus far. Therefore, only a potential signaling pathway from plant mitochondria to the nucleus can be discussed here.

Therein, thioredoxins were found to play a role as mediators of the redox state for plasmid-mitochondria communication and might also take part in mitochondrial signaling to the nucleus (Balmer *et al.* 2004). In addition, reactive oxygen species were also considered as signal molecules from plant mitochondria to the nucleus in relation to environmental stress (Lee *et al.* 2002; Dutilleul *et al.* 2003; Mittler *et al.* 2004). Another signaling pathway involved in the mitochondria-nucleus interaction was the Ca^{2+}-independent signaling pathway, in which mitochondrial respiratory deficiencies triggering novel Ca^{2+}-independent signaling pathway led to constitutively up-regulate heat shock proteins (Kuzmin *et al.* 2004).

DISCUSSION AND PERSPECTIVES

Cytoplasmic male-sterility, or CMS, provides a path to explore the role of mitochondria in vegetative and reproductive development and interactions of the mitochondria-nucleus, apart from its agronomic importance in hybrid production. Indeed, so many mitochondrial CMS-associated causal factors have been identified to date. Likewise, some potential nuclear targeted genes have also been studied in some CMS types. Hence, mitochondrial genes could not directly operate above nuclear targeted genes, and thus there must be a signal pathway inducing male sterility. However, until now no one has been able to respond how and in which pathway the mitochondria-nucleus interaction induces CMS.

In our present investigations, we are trying to answer these questions from a restricted view by using a new *orf220*-type CMS mustard (*Brassica juncea*) developed from distant hybridization (failure of microsoprogenesis type of CMS). We hypothesized one probable pathway for the occurrence of CMS, which was nuclear MADS-like transcriptional factor genes subjected to mitochondrial regulation inducing cytoplasmic male sterility in this type of CMS (**Fig. 1**). To validate this hypothesis, further evidence should be offered about what in fact happens with the above nuclear genes when mitochondrial CMS-associated genes are transferred into fertile plants. Another pathway could be PCD of tapetal cells leading to failure of pollen development induced by the release of cytochrome c in mitochondria (**Fig. 1**). To identify the exact signal pathway, the whole genome should be analyzed in detail and the molecules that interact with mitochondrial CMS-associated genes should also be identified using yeast-two hybridization or other approaches. In addition, mutants with nuclear encoded mitochondrial targeted genes, also exhibiting male sterility, could be another system prone to investigate the interaction of the mitochondria-nucleus interaction in model plants.

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