THE INTERNATIONAL JOURNAL OF SCIENCE & TECHNOLEDGE

Group II Introns of Mitochondria and Nuclear Encoded Maturases Proteins

Sunita Malik
Amity Institute of Biotechnology, Amity University, Haryana, India
K. C. Upadhyaya
Amity Institute of Biotechnology, Amity University, Noida, India
S. M. Paul Khurana
Amity Institute of Biotechnology, Amity University, Haryana, India

Abstract:
The removal of group II introns from plant mtDNA is essential for normal function of mitochondria, thus respiratory functions. Intron encoded maturases are proteins which facilitate self splicing of group II introns in bacteria and organellar genomes of several lower eukaryotes. It was recently found that the nuclear genomes of higher plants bear four genes (nMat 1-4), which are closely related to maturases and contain N-terminal mitochondrial localization signals. The roles of three of these paralogs in Arabidopsis, nMAT1 and nMAT2, nMAT4 in the splicing of mitochondrial introns have been established. In this review, background information on maturases with recent discoveries has been presented.

Key words: *maturase/ group-II/ intron/ splicing/ mitochondria*

1. Mitochondria

Mitochondria are organelles responsible for aerobic energy production in eukaryotic cells (40, 54). Although most of the proteins of mitochondria are coded by nuclear DNA, a number of essential proteins are coded by mitochondrial DNA (mtDNA) that resides within the mitochondria itself (40). In many organisms, including mammals (26) and most flowering plants (63), mtDNA is maternally inherited; it encodes essential subunits of inner mitochondrial membrane respiratory chain complexes, the main function of which is to produce energy, in the form of ATP, from the oxidation of glucose and fatty acids through the process of oxidative phosphorylation (54). Mitochondria are also involved in other cellular functions, such as calcium homeostasis, apoptosis (programmed cell death), iron homeostasis, various pathways of intermediary metabolism and cellular signaling (20).

According to the traditional endosymbiont theory, present day mitochondria evolved from an aerobic bacterium that invaded a primordial eukaryotic cell and became a symbiotic partner that provided metabolic machinery for the complete oxidation of fermentation end products. More recently, it has been theorized that the primordial eukaryote emerged following the fusion of an anaerobic archaebacterium with aerobic respiration-competent alpha-proteobacterium (29, 70). In either case, over evolutionary time, genes were transferred from the genome of the aerobic partner into what became the eukaryotic nucleus, leading, eventually, to the reduced genomes found within the mitochondrion in present day eukaryotes.

2. Mitochondrial DNA

The mitochondrial genome has several unique features relative to the nuclear genome. The organization of mitochondrial DNA (mtDNA) is different from that of nuclear (nDNA), in some organisms its genetic code is different, and its replication is independent of the cell cycle. Furthermore, there is widespread diversity among modern mitochondrial genomes with respect to both their structure and their organization.

2.1. Size and Structure of mtDNA

Regarding the diversity in mtDNA size, structure and gene content, much of our current knowledge comes through the sequencing of over 130 mitochondrial genomes (30). Members of the apicomplexan protozoans possess the smallest mtDNAs, 6 Kbp in size (22); at the other extreme are land plants, whose genomes range up to 2400 Kbp (muskmelon). The structure of mtDNA is quite variable. Typically, vertebrate mtDNA is a circular 16-Kbp DNA molecule that contains 37 genes (11). Even though the most common mtDNA structure is a single circle, multi-circular and linear mtDNAs also exist. For example, the metazoan *Dicyema's* mtDNA consists of a series of 2 to 3-Kbp circles each containing one gene (74). Alternatively, the mitochondrial genomes (mt-genomes) of more than 10 fungi such as *Hyaloraphidiu curvatum* have been shown to be linear (25, 60).

2.2. Gene Content in mtDNA

The extant mt-genomes exhibit not only diversity in size and structure but also variation in gene content. Although the gene number among various mt-genomes varies dramatically from 98 in the protozoan *Reclinomonas americana* (45) to 3 genes in

Plasmodium falciparum (16), most mtDNAs encode a similar set of proteins which can be categorized into two groups. Information processing genes, such as mitochondrial ribosomal RNA (rRNA) genes and transfer RNA (tRNA) genes encompass the first group. The second assortment consists of protein-coding genes that are components of the mitochondrial respiratory chain. Specifically, genes for complex I (*nad*), complex III (*cob*), complex IV (*cox*) and complex V (*atp*) are typically encoded by mtDNAs (31).

Based on the number of mtDNA-encoded genes, mt-genomes can be roughly classified into two general categories: ancestral (minimally diverged) or derived (29). The most extreme example of an ancestral mitochondrial genome is that of the protist *Reclinomonas americana* encoding the largest complement of genes described to date. The large contingent of mtDNA- encoded genes along with the distinct eubacterial nature of several of them supports the view that the *Reclinomonas* mt-genome is ancestral (30, 45). Land plants such as *Marchantia* (a liverwort) also retain a large contingent of genes with a total of 71. Furthermore, land plant mt-genomes accommodate extra genes including a complex II gene, ribosomal protein genes (*rps* and *rpl*) and certain complex I and complex V genes that are not present in the mtDNA of metazoans. Additional identifiable features of ancestral mt-genomes are a standard genetic code, eubacterial-like gene clusters and eubacterial-like rRNA genes (29).

2.3. Plant Mitochondrial Gene Content

In contrast to the vertebrate mt-genomes that are compact and small, the mt-genomes of higher plants exhibit extraordinarily large sizes, extending from 222 Kbp of the *Brassica napus* (*B. napus*) mt-genome (34) up to and over 2000 Kbp for the mt-genomes of some species within the Cucurbitaceae (73). Due to large mtDNA sizes, gene density is relatively low in plant mtDNAs. In *Arabidopsis thaliana (A. thaliana)* and *B. napus*, identified genes account for only 10% of the genome. Introns, duplications, integrations of DNA of nuclear and plastid origin and large unidentified open reading frames (ORFs) account for another 30% (34). In the dicot sugarbeet, 55.6% of the mt-genome has no clear function (42). In the case of two grasses, maize and rice, the scenario repeats itself as non-coding sequences represent 83% and 76% of their mt-genomes, respectively (14). Gene content is also somewhat variable among plant mtDNAs: some individual genes have been transferred to the nucleus in some species whereas in others they remain in the mitochondrial genome. Despite this, a population of genes that encode highly hydrophobic proteins for the complexes of the oxidative respiratory chain and the ATP synthase such as *nad*1, *nad*4, *nad*5, *atp*8, and *atp*6, are consistently maintained within the higher plant's mt-genomes (34).

2.4. Plant Mitochondrial Gene Expression

In addition to, or perhaps as a result of, the complex mt-genomes in plants, regulation of gene expression of this organelle has distinctive features. Plant mitochondrial RNA polymerases and promoters, as well as post-transcriptional and translational controls, including 5' and 3' stability, *cis*- and *trans*-splicing, and RNA editing have been the subjects of several reviews (7, 35).

2.5. Post-Transcriptional Regulation

Transcription is only the first step in determining the steady-state population of translatable RNA. Post-transcriptional events such as 5' and 3' termini processing via nuclease activity, *cis*-splicing, *trans*-splicing, and RNA editing are also important in plant mitochondria.

2.6. RNA Editing

RNA editing is a feature of plant mitochondria gene expression, where specific C's in the primary transcript are converted to U's post-transcriptionally. The first case of RNA editing was discovered in 1986 and involved the addition and deletion of uridine residues in the RNAs of the kinetoplast, the mitochondria of trypanosomes (6). In 1989, cytosine to uracil editing was reported in angiosperm mitochondria by several laboratories (32, 17). The discovery had resulted from comparing DNA and messenger RNA (mRNA) sequences of several mitochondrial genes. Analysis of cytochrome oxidase subunit II gene (*cox2*) sequences had shown that some extremely conserved tryptophan residues (UGG) of *cox2* were replaced by a CGG triplet which usually encodes the amino acid arginine (24). However, it was intriguing that only a small fraction of CGG triplets behave abnormally. Following the discovery of editing in plant mitochondria it was recognized that editing led to the conversion of some of these CGG's to the expected UGG triplet that "universally" codes for tryptophan. No editing process was found to occur in the bryophyte *Marchantia* (61) although editing appears to be operative in the chloroplasts and the mitochondria of other bryophytes; interestingly, in the latter case, both U to C as well as C to U modifications were observed (49).

A global investigation of editing sites in the *A. thaliana* mitochondria was conducted by Giegé and Brennicke in 1999. A total of 441 editing sites were found, mostly located in coding regions; some were found to occur in introns and leader or trailer sequences, but were very rare elsewhere. In a similar investigation performed in *B. napus*, Handa (2003) discovered 427 sites, 81% of which were shared with *A. thaliana*. Compared to the average DNA sequence similarity for protein coding genes of 9.2% between these closely related species, diversification of editing seems higher than the diversification of coding information. In neither of these surveys of editing sites could common sequence elements for editing be found. Electroporation experiments indicate that *cis* elements 20 nucleotides upstream of the editing site could help define editing sites (21).

Although most of the editing sites reported corresponded to amino acids differing from those deduced from the gene as well as to the creation of initiation or stop codons, some silent editing events not leading to the change of the encoded amino acid have been described in several plant mitochondrial mRNAs. The reason for silent editing is still unknown. While RNA editing is abundant in mitochondrial mRNAs, some C to U events involve organellar tRNAs and some intronic regions (76). In the case of tRNAPhe, editing is absolutely necessary to produce the macromolecule from a longer precursor transcript (50, 51).

Incompletely edited transcripts have also been detected. Recent results have shown that partially edited transcripts may be found in the polysomal fractions. Moreover, polymorphic proteins produced from partially edited mRNAs have been identified in the

case of maize mitochondrial *rps*12 (47). These authors have speculated that while the edited ribosomal protein is inserted in the ribosomal unit, the unedited form, found in the polysomal supernatant, may act as an RNA binding protein.

2.7. Cis- and Trans-Splicing

Coding sequences in plant mitochondrial genes are frequently interrupted by introns that are removed post-transcriptionally by RNA splicing (9, 26, 65). Group I and group II introns are large self-splicing ribozymes. In contrast to group I introns, group II intron excision occurs in the absence of GTP and involves the formation of a lariat, with an adenosine residue branchpoint strongly resembling that found in lariats formed during splicing of nuclear pre-mRNA (see below). Both group I and group II introns are found in plant mitochondrial genes and plant mitochondrial group II introns are found in either *cis* or *trans* configuration (57). Many group II introns in plants differ markedly from the canonical group II intron structural framework. Some lack elements that are considered to be essential to the formation of the catalytic center, and some have become fragmented during the course of evolution such that they are transcribed in pieces that must then be *trans*-spliced (48). Examples of group II *trans*-splicing occur in the *C. reinhardtii* chloroplast *psa*A mRNA (13, 43), in the angiosperm mitochondrial *nad*1, *nad*2, and *nad*5 mRNAs (10, 39). The *trans*-spliced intron fragments represent structural modules that assemble with one another via RNA-RNA interactions to recreate an intact group II intron structure. The efficiency and fidelity of this complex recognition process seem likely to be aided by protein cofactors, and there is genetic evidence for the participation of many proteins in the *trans*-splicing of the *psa*A introns in *C. reinhardtii* chloroplasts (28).

3. Group I and II introns

Introns of organellar genomes, including those of plant mitochondria, can be divided into two main groups (I and II) (54, 8, 77, 44, 9) that differ by a number of criteria, such as differences in their predicted secondary structures and the mechanism by which some introns of both groups can undergo self-splicing *in vitro*. In land plant mitochondria, protein-coding genes frequently contain group I and group II introns (46). In *Marchantia* mtDNA, 32 introns, including both group I and group II introns, are present (61), whereas most of the 25 introns identified to date in flowering plant mitochondria (42, 34) are group II introns.

Group I introns contain a set of conserved sequence elements that are involved in folding such a way that the exons are positioned closely together in space and splicing can occur (59). Some group I introns can undergo autocatalytic or self-splicing: splicing in the absence of any protein co-factor that requires no RNA other than the intron itself. Group I intron self splicing occurs via a transesterification mechanism (the process of exchanging the alkoxy group of an ester compound by another alcohol), initiated by an attack of a guanosine nucleotide at the 5' end of the intron; the liberated 3'- hydroxyl group of the 5' exon then attacks the 3' splice junction, resulting in exon ligation and intron release.

Group II introns are large, natural ribozymes found in prokaryotes and eukaryotic organelles (mitochondria, chloroplast); they are identified by characteristic primary, secondary and tertiary RNA structural elements (53). The splicing of group II introns involves two successive trans- esterification reactions between RNA nucleotides leading into joining of two exons and releasing the typical intron lariat in a manner identical to the eukaryotic intron splicing (Figure 1). Group II splicing is initiated by the 2'-hydroxyl group of a "bulged" adenosine residue in the domain 6 helix, which attacks the 5' splice junction. The covalent attachment of the 2'-hydroxyl group to the 5' intron residue results in a branched structure called as a lariat, and the attacking adenosine is called the "branchpoint". The 3'-hydroxyl of the cleaved 5' exon then attacks the 3' splice junction, resulting in exon ligation and release of the intron as a lariat structure. Some structural elements of group II introns resemble those of eukaryotic spliceosomal snRNA which is consistent with the premise that the group II introns are the evolutionary precursors of eukaryotic spliceosomes (23, 68, 72, 77).

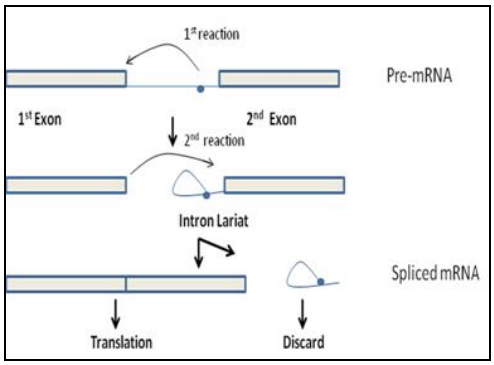

Figure 1

Figure 1: Splicing of group II introns involves a two-step biochemical process. Both steps involve transesterification reactions that occur between RNA nucleotides. In the first step, a bulged adenosine in domain 6 attacks the 5' splice site junction, resulting in cleavage of the 5' exon and formation of a lariat intermediate. In the second step, the 5'and 3' exons are ligated together and the intron is released as a lariat.

In vitro, some group II introns can splice autocatalytically without requiring any additional protein but *in vivo* all are thought to require accessory proteins for efficient splicing. The best known of these accessory proteins are the maturases, which in most cases, are encoded within the intron itself. Structurally, group II introns fold into a conserved secondary structure which consists of six domains (dI- dVI or D1-D6) that radiate from a central wheel and bring the 5' and 3' splice junction into close proximity (62, 53). The largest domain is domain 1, which is thought to deliver the molecular scaffold assembling the intron in its active

structure, while domain 5 is the phylogenetically most conserved part and represents the active site of the ribozyme (53). Multiple interactions between different domains are required to stabilize the tertiary structure of group II introns into their catalytically active forms (67) Plant mitochondrial group II introns are found either in a *cis* or *trans* configuration (57). *Cis*-splicing processes a single molecule where two exons are joined together by the removal of an intervening intron sequence. t*rans*-splicing processes two different RNA transcripts and joins the two exons to produce one mature transcript. Group II introns can be further divided into groups IIA and IIB according to differences in the structure and the mechanism of splicing (46).

4. The Spliceosome

Spliceosome is a complex of specialized RNA and protein subunits (ribonucleoprotein machinery) that removes introns from a transcribed pre-mRNA (hnRNA) segment during splicing. The spliceosome is composed of 20 proteins and five RNA components, U1, U2, U4, U5, and U6 snRNAs, which share both structural and functional similarities with group II introns (69). From the five snRNAs, U1 and U4 leave the spliceosome prior to splicing catalysis and U5 helps to align the exons. U2 and U6 are the only two snRNAs needed for the splicing steps. Comparative analysis of the U6/U2 complex revealed striking similarities with D5 and D6 of group II introns (63).

Currently, it is believed that the primary role of U2 snRNA is to position internal adenine nucleophile for the initial trans-esterification reaction. Deletion of D6 in group II introns drives the splicing via hydrolysis rather than trans-esterification (52). So U2 by default might not play a direct role in catalysis. The secondary structure of U6 shows a GRNA-type lock capping helix, an internal bulge, and an ACG triad (63). These secondary structures of U6 are structurally similar with domain 5 of group II introns (63). These structural equivalents have helped further the idea that the modern spliceosome originated from group II introns.

5. Maturases

Most group II intron maturases are encoded by the intron themselves, but some are encoded by other genes of the host organism (in the case of bacteria and higher plant mitochondria) or organelle (chloroplasts, plant and fungal mitochondria). Maturases function not only to promote splicing, but also the retrotransposition of the released intron into related genomic sites. Yeast mitochondrial *coxI*-I1 and I2 group II introns and the *Lactococcus lactis* L1.LtrB group II intron have been studied extensively and biochemical activities of the intron-encoded proteins (IEPs) are known (12, 52).

Most maturases contain conserved domains (Figure 2) involved in reverse transcription of the intron (RT), intron-RNA binding (X), DNA binding (D) and DNA endonuclease activity (En). Among these, the RT, D, En domains are involved in intron mobility and the RT and X domains are involved in splicing (12, 52). Generally, maturases mediate the splicing and retrotransposition of only the introns that encode them, or of closely related introns.

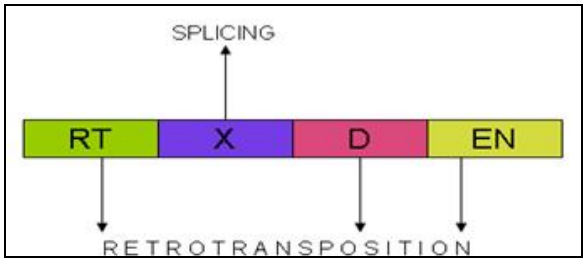

Figure 2

Figure 2: Domains of maturases involved in intron splicing and retrotransposition. The RT domain specifies reverse transcription activity, the X domain functions in RNA binding associated with splicing, the D domain functions in DNA binding domain associated with reverse transcriptase activity, and the En domain specifies an endonuclease involved in reverse transcriptase activity. D and En also function in aspects of retrotransposition other than reverse transcription.

Although the organellar introns in plants have probably evolved from maturase-encoding group-II introns (3), angiosperm mitochondrial genomes has retained only a single gene, *mat*R, encoding a maturase-like protein designated as Maturase-Related (MAT-R) (66). MAT-R is encoded within within *nad*1 intron 4. RNA editing events increase the similarity of the encoded protein to other maturases ORF. MAT-R is expected to encode a functional protein, as it has been retained in the mtDNA in all angiosperms (2, 19, 33) suggesting that *mat*R encodes a functional protein. There is no direct evidence, however, that *mat*R encodes a functional protein. In addition to maturases, a number of other proteins are required for group II intron splicing in different organisms (44). For example, several plant genes designated as CRSs (Chloroplast RNA Splicing) have been found to be involved in the splicing of a number of chloroplast group II introns.

Lately, four maturase-like proteins were identified in the *A. thaliana* nuclear genome (22). The proteins encoded by these genes are termed nuclear maturases (n*Mat*) and were predicted to splice group II introns in mitochondria. The four n*Mat* genes are classified as n*Mat*1 (At1g30010), n*Mat*2 (At5g46920), n*Mat*3 (At5g04050), and n*Mat*4 (At1g74350) (37, 38, 56). The NMat proteins are predicted to have mitochondrial localization signals and a conserved X domain suggesting that these putative maturases are transported to the organelle and may function in the splicing of group II introns. Orthologs of all four n*Mat* genes are found in rice genome and cDNAs have been found for two of the four genes of the *A. thaliana*, suggesting that they encode functional proteins (56). In plant mitochondria there are 22 mitochondrial group II introns but only one, *nad*1i4, encodes a maturase, MatR (29). Since maturases are, in general, highly specific with respect to the intron they interact with, it is unlikely

that the MatR maturase can function in the splicing of all 22 mitochondrial introns. It thus seemed that nMAT proteins were likely to be involved in the splicing of at least some plant mitochondrial introns.

In Arabidopsis, maturases seem particularly important for the maturation of primary *nad*1 transcripts. Homozygote *nmat* mutants show altered growth and developmental phenotypes, modified respiration and altered stress responses, which are tightly correlated with mitochondrial complex I defects (37, 58). While nMAT1 is required in trans-splicing of *nad*1 intron 1, *nad*2 intron 1 and *nad*4 intron 2 (37), nMAT2 functions in the efficient splicing of *nad*1 intron 2, *nad*7 intron 1 and the single intron in the cytochrome oxidase subunit 2 gene (*cox*2 intron 1) (37), nMAT4 functions in efficient processing of *nad*1 intron 1, 3 and 4 (15). The accurate biochemical functions of nuclear-encoded maturases in the splicing process have not yet been established. At present there is no report on nMAT3.

6. Evolution of the Mitochondrial Genome

Extensive gene loss by mitochondrial genomes has occurred in all eukaryotic lineages. It is not unexpected that the hypothetical ancestor of mitochondrion would lose genes required by the free living organism. Moreover, once the process of gene loss began, it may have accelerated because it could have provided a means of enabling nuclear coordination of expression of mitochondrial gene expression and thus nuclear control over mitochondrial function (75). Several theories have been formulated to describe why mitochondria have maintained certain genes in all lines of descent, and not allowed for complete transfer of genes to the nucleus. The hydrophobicity hypothesis states that because the most conserved mitochondrial gene products are also among the most hydrophobic proteins, import of these proteins from the cytoplasm may have been difficult, thus preventing the transfer of the genes encoding them to the nucleus (71). A second theory suggests that the change in genetic code between nuclear and mitochondrial genomes, especially the common change of UGA to code for tryptophan in mitochondria instead of a stop codon, would lead to severe truncation in proteins or amino acid substitutions and thus being selected against gene transfer (36). This codon change appears to have occurred after the loss of the majority of genes, so it may be involved in maintenance of the now heavily reduced mitochondrial chromosomes (18). Lastly, the location based expressional control theory states that key genes involved in oxidative phosphorylation are expressed in the mt-genome so that their proximity to the enzyme complexes may regulate their expression (1, 4, 5).

On the basis of the structural features, the similarity in exon-intron boundaries and a common splicing mechanism, group II introns are proposed to be ancestors of the eukaryotic spliceosomal introns. While only a single intron maturase has been retained in the two organelle genomes of angiosperms, several other maturase genes have been transferred into the nucleus during the evolution of plants. It seems that a group II intron invaded the eukaryotic cell nucleus, possibly derived from the mitochondrial symbiont and served as the evolutionary precursor to the nuclear splicesomal introns.

7. References

1. Adams, K.L., Palmer, J.D. (2003). Evolution of mitochondrial gene content: gene loss and transfer to the nucleus. Molecular Phylogenetic Evolution, 29, 380-395.
2. Adams, K.L., Qiu, Y.L., Stoutemyer, M. and Palmer, J.D.(2002). Inaugural Article: Punctuated evolution of mitochondrial gene content: High and variable rates of mitochondrial gene loss and transfer to the nucleus during angiosperm evolution. Proceedings of the National Academy of Sciences, 99, 9905-9912.
3. Ahlert, D., Piepenburg, K., Kudla, J. and Bock, R. (2006). Evolutionary origin of a plant mitochondrial group II intron from a reverse transcriptase/maturase-encoding ancestor. Journal of Plant Research, 119, 363-371.
4. Allen, J.F. (1993). Control of gene expression by redox potential and the requirement for chloroplast and mitochondrial genomes. Journal of Theoretical Biology, 165, 609-631.
5. Allen, J.F. (2003). The function of genomes in bioenergetic organelles. Philosophical Transactions of the Royal Society B , 358, 19-37.
6. Benne, R., Van den Burg, J.V.D., Brakenhoff, J.P., Sloof, P., Van Boom, J.H., Tromp, M.C. (1986). Major transcript of the frameshifted coxII gene from trypanosome mitochondria contains four nucleotides that are not encoded in the DNA. Cell, 46-6, 819-826.
7. Binder, S., Marchfelder, A., and Brennicke, A. (1996). Regulation of gene expression in plant mitochondria. Plant Molecular Biology, 32, 303-314.
8. Bonen, L., and Vogel, J. (2001). The ins and outs of group II introns. Trends Genetics, 17, 322-331.
9. Bonen, L. (2008). Cis- and trans-splicing of group II introns in plant mitochondria. Mitochondrion, 8, 26-34.
10. Bonen, L. (1991). The mitochondrial genome: so simple yet so complex. Current Opinion in Genetetics and Development, 1, 515-522.
11. Boore, J.L. (1999) Animal mitochondrial genomes. Nucleic Acids Research, 27, 1767-1780.
12. Carigiani, G., Groudinsky, O., Frezza, D., Schiavon, E., Bergantino, E.,
13. Slonimski, P. P. (1983). An mRNA Maturase is encoded by the first intron of the mitochondrial gene for the subunit I of cytochrome oxidase in S.servisiae. Cell, 35, 733-742.
14. Choquet, Y., Goldschmidt-Clermont, M., Girard-Bascou, J., Kuck, U., Bennoun, P., and Rochaix, J.D. (1988). Mutant phenotypes support a trans-splicing mechanism for the expression of the tripartite psaA gene in the C.reinhardtii chloroplast. Cell, 52, 903-913.
15. Clifton, S.W., Minx, P., Fauron, C.M.R., Gibson, M., Allen, O.J., Sun, H., Thompson, M., Barbazuk, W.B., Kanuganti, S., Tayloe, C., Meyer, L., Wilson, R.K., Newton, K.J. (2004). Sequence and comparative analysis of the Maize NB mitochondrial genome. Plant Physiology, 136, 3486-3503.

16. Cohen, S., Zmudjak, M., Small, C.C.D.F., Malik, S., Shaya, F., Keren, I., Belausov, E., Mani, Y., Brown, G.G, Small, I., Ostersetzer-Biran, O. (2013). nMAT4, a maturase factor required for nad1 pre-mRNA processing and maturation, is essential for holocomplex I biogenesis in Arabidopsis mitochondria. The Plant Journal, in press.
17. Conway, D.J., Fanello, C., Lloyd, J.M., Al-Joubori, B.M., Baloch, A.H., Somanath, S.D., Roper, C., Oduola, A.M., Mulder, B., Povoa, M.M., Singh, B., Thomas, A.W. (2004). Origin of Plasmodium falciparum malaria is traced by mitochondrial DNA. Mol Biochem. Parasitol., 111, 163-171.
18. Covello, P.S., and Gray, M.W., RNA editing in plant mitochondria. Nature, 1989, 341, 662-666.
19. de Grey, A.D. (2005). Forces maintaining organelar genomes: is any as strong as genetic code disparity or hydrophobicity? Bioessays, 27, 436-446.
20. Dombrovska, O. and Qiu, Y.L. (2004). Distribution of introns in the mitochondrial gene nad1 in land plants: phylogenetic and molecular evolutionary implications. Molecular Phylogenetics and Evolution, 32, 246-263.
21. Ernster, L., and Schatz, G. (1981). Mitochondria: a historical review. The journal of scientific biology, 91-3, 227-255.
22. Farré, J.C., Leon, G., Jordana, X., and Araya, A. (2001). Cis recognition elements in plant mitochondrion RNA editing. Molecular Cell Biology, 21, 6731-6737.
23. Feagin, J.E.(1994). The extrachromosal DNAs of apicomplexan parasite. Annual Reviews of Microbiology, 48, 81-104.
24. Ferat, J.L., and Michel, F.(1993). Group II self-splicing introns in bacteria. Nature, 364, 358-361.
25. Fox, T.D., and Leaver, C.J. (1981). The Zea mays mitochondrial gene coding cytochrome oxidase subunit II has an intervening sequence and does not contain TGA codons. Cell, 26, 315-323.
26. Fukuhara, F. S., Drissi, R., Dinouël, N., Miyakawa, I., Rousset, S., and Viola, A.M.(1993). Linear mitochondrial DNAs of yeasts: frequency of occurrence and general features. Molecular Cell Biology, 13, 2309-2314.
27. Gagliardi, D., and Binder, S., Expression of the plant mitochondrial genome. In Plant Mitochondria, (ed. D. Logan), Blackwell Publishing, Ames, IA, 2007, 50-95.
28. Giles, R.E., Blanc, H., Cann, H.M., Wallace, D.C. (1980). Maternal inheritance of human mitochondrial DNA. Proceedings of National Acadamy of Science, 77, 6715-6719.
29. Goldschmidt-Clermont, M., Girard-Bascou, J., Choquet, Y., Rochaix, J.D. (1990). Trans-splicing mutants of Chlamydomonas reinhardtii. Molecular and Genetics and Genomics, 223-3, 417-425.
30. Gray, M.W., Burger, G., Lang, B.F. (1999). Mitochondrial evolution. Science, 283, 1476-1481.
31. Gray, M.W., Lang, B.F., Cedegren, R., Golding, G.B., Lemiux, C., Sankoff, D., Turmel, M., Brossard, N., Delage, E., , T.G., Plante, I., Rioux, P., Saint-Louis, D., Zhu, Y., Burger, G. (1998). Genome structure and gene content in protist mitochondrial DNAs. Nucleic Acids Research, 26, 865-878.
32. Gray, M.W., Spencer, D.F.(1996). Organellar evolution in evolution of microbial life. Cambridge University Press, 109-126.
33. Gualberto, J.M., Lamattina, L., Bonnard, G., Weil, J.L., Grienenberger, J. M. (1989). RNA editing in wheat mitochondria results in the conservation of protein sequences. Nature, 341, 660-662.
34. Guo, W. and Mower, J. (2013). Evolution of plant mitochondrial intron-encoded maturases: frequent lineage-specific loss and recurrent intracellular transfer to the nucleus. Journal of Molecular Evolution, 77, 43-54.
35. Handa, H. (2003). The complete nucleotide sequence and RNA editing content of the mitochondrial genome of rapeseed (Brassica napus L.): comparative analysis of the mitochondrial genomes of rapeseed and A. thaliana. Nucleic Acids Research, 31, 5907-5916.
36. Hofmann, M., Kuhn, J., Daschner, K., Binder, S. (2001). The RNA world of plant mitochondria. Progress in Nucleic Acids Research and Molecular Biology, 70, 119-154.
37. Jacobs, H.T. (1991). Structural similarities between a mitochondrialy encoded polypeptide and a family of prokaryotic respiratory toxins involved in plasmid maintenance suggest a novel mechanism for the evolutionary maintenance of mitochondrial DNA. Journal of Molecular Evolution, 32, 333-339.
38. Keren, I., Bezawork-Geleta, A., Kolton, M., Maayan, I., Belausov, E., Levy, M., Mett, A., Gidoni, D., Shaya, F., Ostersetzer-Biran, O. (2009). AtnMat2, a nuclear-encoded maturase required for splicing of group-II introns in Arabidopsis mitochondria. RNA, 5-12, 2299-2311.
39. Keren, I., Tal, L., des Francs-Small, C.C., Araújo, W.L., Shevtsov, S., Shaya, F., Fernie, A.R., Small, I. and Ostersetzer-Biran, O. (2012). nMAT1, a Nuclear-encoded Maturase involved in the trans-splicing of nad1 intron 1, is essential for mitochondrial complex I assembly and function. Plant Journal, 71, 413-426.
40. Knoop, V., Malek, O., Brennicke, A. (1997). Evolution of tans-splicing plant mitochondrial introns in pre-permian times. Proceedings of National Acadamy of Science, 94, 553-558.
41. Knoop, V. (2012). Seed Plant Mitochondrial Genomes: Complexity Evolving. In Genomics of Chloroplasts and Mitochondria (ed. Bock and Knoop), Springer, 175-195.
42. Krebs, H., and Johnson, W.A. (1937). The role of citric acid in intermediate metabolism in animal tissues. Enzymologia, 4, 148-156.
43. Kubo, T., Nishizawa, S., Sugawara, A., Itchoda, N., Estiati, A., and Mikami, T. (2000). The complete nucleotide sequence of the mitochondrial genome of sugar beet (Beta vulgaris L.) reveals a novel gene for tRNACys (GCA). Nucleic Acids Research, 28, 2571-2576.
44. Kück, U., Choquet, Y., Schneider, M., and Bennoun, P. (1987). Structural and transcription analysis of the two homologous genes for the P700 chlorophyll a-apoprotein in Chlamydomonas reinhardtii: evidence for in vivo trans-splicing. EMBO Journal, 6, 2185-2195.
45. Lambowitz, A.M., and Zimmerly, S. (2004). Mobile group II introns, Annual Reviews of Genetics, 38, 1-35.

46. Lang, B.F., Gray, M.W., Cedegren, R., Burger, G., Golding, G.B., Lemiux, C., Sankoff, D., Turmel, M. (1997). An ancestral mitochondrial DNA resembling a eubacterial genome in miniature. Nature, 387, 493-497.
47. Lehmann, K., and Schmidt, U., Group II Introns: Structure and catalytic versatility of large natural ribozymes. Critical Review in Biochemistry and Molecular Biology, 2003, 38, 249-303.
48. Lu, B., Wilson, R.K., Phreaner, C.G., Mulligan, R.M., and Hanson, M.R. (1996). Protein polymorphism generated by differential RNA editing of a plant mitochondrial rps12 gene. Molecular Cell Biology, 16-4, 1543-1549.
49. Malek, O., and Knoop, V. (1998). Trans-splicing group II introns in plant mitochondria: the complete set of cis-arranged homologs in ferns, fern allies, and a hornwort. RNA, 4, 1599-1609.
50. Malek, O., Lättig, K., Hiesel, R., Brennicke, A., and Knoop, V. (1996). RNA editing in bryophytes and a molecular phylogeny of land plants. EMBO Journal, 15-6, 1403-1411.
51. Marchfelder, A., Brennicke, A., and Binder, S. (1996). RNA Editing is required for efficient excision of tRNA Phe from precursors in plant mitochondria. The Journal of Biological Chemistry, 271, 1898-1903.
52. Maréchal-Drouard, L., Cosset, A., Remacle, C., Ramamonjisoa, D., and Dietrich, A. (1996). A single editing event is a prerequisite for efficient processing of potato mitochondrial phenylalanine tRNA. Molecular Cell Biology, 7-16, 3504-3510.
53. Matsuura, M., Saldanha, R., Wank, H., Yang, J., Mohr, G., Cavanagh, S., Dunny, G.M., Belfort, Lambowitz, A.M. (1997). A bacterial group II intron encoding reverse transcriptase, maturase, and DNA endonuclease activities: biochemical demonstration of maturase activity and insertion of new genetic information within the intron. Genes and Development, 11, 2910-2924.
54. Michel, F., and Ferat, J.L. (1995). Structure and activities of group II introns. Annual Reviews of Biochemistry, 64, 435-461.
55. Michel, F., Umesono, K., and Ozeki, H. (1989). Comparative and functional anatomy of group II catalytic introns - a review. Gene, 82, 5-30.
56. Mitchell, P., Coupling of phosphorylation to electron and hydrogen transfer by a chemi-osmotic type of mechanism. Nature, 1961, 191, 144-148.
57. Mohr, G., and Lambowitz, A. (2003). Putative proteins related to group II intron reverse transcriptase/maturases are encoded by nuclear genes in higher plants. Nucleic Acids Research, 31-2, 647-652.
58. Morawala-Patell, V., Gualberto, J.M., Lamattina, L., Grienenberger, J.M., Bonard, G. (1998). Cis- and trans-splicing and RNA editing are required for the expression of nad2 in wheat mitochondria. Molecular Genetics, 258, 503-511.
59. Nakagawa, N., and Sakurai, N. (2006). A Mutation in At-nMat1a, which encodes a nuclear gene having high similarity to group II intron maturase, causes impaired splicing of mitochondrial nad4 transcript and altered carbon metabolism in A. thaliana. Plant Cell Physiology, 47-6, 772-783.
60. Nesbo, C.L., and Doolittle, W.F. (2003). Active self-splicing group I introns I 23 rRNA genes of hyperthermophilic bacteria, derived from introns in eukaryotic organelles. Proc. Nat. Acad. Sci. U S A, 100, 10806-10811.
61. Nosek, J., Tomaska, L., Fukuharac, H., Suyama, Y., and Kovac, L. (1998). Linear mitochondrial genomes: 30 years down the line. Trends in Genetics, 14, 184-188.
62. Oda, K., Yamato, K., Ohta, E., Nakamura, Y., Takemura, M., Nozato, N., Akashi, K., Kanegae, T., Ogura, Y., Kohchi, T. (1992). Gene organization deduced from the complete sequence of liverwort Marchantia polymorpha mitochondrial DNA. A primitive form of plant mitochondrial genome. Journal of Molecular Biology, 223-1, 1-7.
63. Saldanha, R., Mohr, G., Belfort, M., and Lambowitz, A.M. (1993). Group I and group II introns. The Federation Of American Societies For Experimental Biology J., 7, 15-24.
64. Sashital, D.G., Cornilescu, G., Butcher, S.E., McManus, C.J., Brow, D.A. (2004). U2-U6 RNA fording reveals a group II intron-like domain and a four-helix junction. Nature Structural & Molecular Biology, 11, 1237-1242.
65. Sodmergen, Zhang Q., Zhang, Y., Sakamoto, W., Kuroiwa, T., Reduction in amounts of mitochondrial DNA in the sperm cells as a mechanism for maternal inheritance in Hordeum vulgare. Planta, 2002, 216, 235-244.
66. Takenaka, M., Verbitskiy, D., van der Merwe, J.A., Zehrmann, A., and Brennicke, A. (2008). The process of RNA editing in plant mitochondria. Mitochondrion, 8, 35-46.
67. Thomson, M.C., Macfarlane, J.L., Beagley, C.T., Wolstenholme, D.R. (1994) .RNA editing of mat-r transcripts in maize and soybean increases similarity of the encoded protein to fungal and bryophyte group II intron maturases: evidence that mat-r encodes a functional protein. Nucleic Acids Research, 22-25, 5745-5752.
68. Toor, N., Keating, K.S., Taylor, S.D., and Pyle, A.M. (2008). Crystal structure of a self-spliced group II intron. Science, 320, 77-82.
69. Toro, N. (2003). Bacteria and archaea group II introns: additional mobile genetic elements in the environment. Environmental Microbiology, 5, 143-151.
70. Valadkhan, S., Mohammadi, A., Wachtel, C., Manley, J.L. (2007). Protein-free spliceosomal snRNAs catalyze a reaction that resembles the first step of splicing. RNA, 13-12, 2300-2311.
71. Vellai, T., and Vida, G. (1999). The origin of eukaryotes: the difference between prokaryotic and eukaryotic cells. Proceedings of the Royal Society B: Biological Sciences, 266, 571-1577.
72. Von Heijne, G. (1986). Why mitochondria need a genome. Federation of European Biochemical Societies, 98, 1-4.
73. Wank, H., SanFilippo J., Singh R.N., Matsuura M., Lambowitz A.M. (1999). A reverse transcriptase/maturase promotes splicing by binding at its own coding segment in a group II intron RNA. Molecular Cell, 4, 239-250.
74. Ward, B.L., Anderson, R.S., Bendich, A.J. (1981). The mitochondrial genome is large and variable in a family of plants (cucurbitaceae). Cell, 25, 793-803.

75. Watanabe, K.I., Bessho, Y., Kawasaki, M., and Hori, H. 1999. Mitochondrial genes are found on minicircle DNA molecules in the mesozoan animal Dicyema. Journal of Molecular Biology, 386, 645-650.
76. Yamauchi, A. (2005). Rate of gene transfer from mitochondria to nucleus: effects on cytoplasmic inheritance system and intensity of intracellular competition. Genetics, 171, 1387-1396.
77. Zanlungo, S., Quiñones, V., Moenne, A., Holuigue, L., and Jordana, X. (1995). Splicing and editing of rps10 transcripts in potato mitochondria. Current Genetics, 27, 565-571.
78. Zimmerly, S., Hausner, G., Wu, X. (2001). Phylogenetic relationships among group II intron ORFs. Nucleic Acids Research, 29, 1238-1250