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Mitochondrial genetic transformation via biotechnological approaches or natural competence mechanism: do we have a choice?

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Regardless quite assertive proofs of horizontal gene transfer into plant mitochondria, the phenomenon existent in many organisms, this field of research still lacks comprehensive information about the mechanism of gene transfer into mitochondria. Up to now, such questions as how nucleic acids traverse mitochondrial membranes and maintain stability in the mitochondrial genome remain the focus of such researches. Circular and especially linear plasmids present in mitochondria of many plant species could be a convinient tool to investigate the mechanisms of mitochondrial membrane DNA transfer and serve as mitochondrial integrative vectors.

Keywords: mitochondrial transformation, DNA import, mitochondrial plasmids, mitochondrial membrane.

The transformation of mitochondria *in vivo* is a fundamental scientific problem of a significant biomedical and biotechnological interest. However, up to the present, the resolution of this problem is still unachievable. The main complications of mitochondrial transformation are (*i*) the small size of mitochondria which makes it difficult to deliver DNA inside the organelles by methods which are in use for chloroplast transformation (bioballistic method); (*ii*) the absence of a relevant gene-reporter, which would allow to select the transformed mitochondria; (*iii*) the presence of numerous mitochondria population in each cell, which is an obstacle for manifesting the transformed genotype at the level of a whole cell. It is important to mention also that for getting inside the mitochondria, nucleic acids must be transferred through the hydrophobic cellular and mitochondrial membranes. Inside mitochondria the foreign DNA must be maintained at steady level either by autonomous replication or by being incorporated into the high molecular weight mitochondrial DNA (via recombination) and, at last, imported DNA must be expressed and provide some selective advantage of the transformed mitochondria in heteroplasmic population of organelles in whole cell.

The attempts of mitochondrial transfection of eukaryotes have being undertaken throughout the last two and a half decades. Various methods were tested both to deliver DNA into mitochondria and to make the mitochondrial genome to express the introduced genetic material. The methodical approaches of mitochondrial transformation *in vivo* were such as (1) bioballistics, this method was limited by using budding yeast and *Chlamydomonas reinhardtii* [1–4]; (2) cell biology approach, when cells deprived of nucleus but carrying mitochondrial DNA with certain traits, were merged with cells without mtDNA [5, 6]; (3) microinjection of recipient cells by mitochondria containing DNA with certain genetic characteristics [5, 7, 8]; (4) co-incubation of mitochondria with ^{0} cells [9, 10]; (5) using of specific carriers: cell incubation with dequalinium particles [11, 12] or mitochondriotropic liposomes [4] loaded with DNA; (6) protein transformation, when DNA is

linked to hybrid protein, consisting of transduction part, which accommodates the mitochondrial transport, and of a TFAM factor [13–15].

The more effective attempts of allogenic DNA transportation into mitochondria are based on the usage of isolated organelles. To deliver DNA into isolated mitochondria *in organello*, several approaches were tested: (1) translocation of protein-DNA conjugates [16, 17] or of PNA-DNA complexes [18] by means of protein mitochondrial transport machinery; (2) electroporation [19–23]; (3) bacterial transfection [24]; (4) mechanism of a natural mitochondrial competence [25–27].

It is known that a natural mechanism of mitochondrial RNA molecules transport exists in many eukaryote organisms (review [28]). This RNA, which is necessary for mtDNA replication and expression, is formed as a result of appropriate nuclear genes expression and imported into mitochondria by mechanisms differing for various organisms. Those mechanisms include some elements of protein (for yeast and mammals [29]) or nucleotide (for plants [30]) mitochondrial transport. Plant and trypanosome mitochondria import from cytosol several tRNA absent in mitochondrial genome, mammalian mitochondria import 5S rRNA, the component of RNase P [31].

Using the phenomenon of $tRNA^{Lys}$ natural mitochondrial transport in yeast, by Kolesnikova et al. [32] it was shown that the import of modified $tRNA^{Lys}$ into mitochondria of human cell culture manifesting the mitochondrial translation defect MERRF can partially restore mitochondrial functions.

At first, the attempts of DNA delivery into isolated mitochondria were based mostly on using either the protein transport machinery accommodating the transport of nucleic acid through the mitochondrial membrane [17] or the electroporation [19]. Specific genetic constructs, which represented DNA-protein complexes, containing mitochondrial protein signal peptides, were expressed in cytosol in order to transfer DNA into mitochondria via mechanism of protein transport [18, 16]. The same mechanism was supposed to be involved in transfer of synthetic PNA molecules, combining the features of proteins (chemical link) and of nucleic acids (nucleotide bases).

As a whole, those approaches are difficult enough technically and, as it was shown practically, had little effectiveness *in vivo* applications. Only in one of the studies, authors [21] showed functionality of the DNA imported into mitochondria with the help of electroporation, namely, transcription and editing of RNA, transcribed from the xenogenic genetic material. In this study, the isolated plant mitochondria were used.

The distinctive features of plant mitochondria are sizes of their genomes, which are several-fold greater than those of other eukaryotes, and the presence of subgenomic molecules and plasmid-like DNAs, replicated autonomously of the main mitochondrial genome (Table). Those particularities allows to assume that plant mitochondria might possess a mechanism of a natural competence to uptake foreign DNA, resembling that of the process in bacterial cells. The preliminary proofs of such a DNA mitochondrial transport mechanism existence in plants were gained by using of bacterial vectors as both vehicles and templates in the system of mitochondrial DNA and RNA synthesis [58, 59]. Further studies showed that mitochondria, isolated not only from various plant species (potato, maize, cauliflower, tobacco cell suspension culture), but also from mammals (rat liver, human cell cultures) are capable to import double-stranded linear DNA molecules of a reasonable size (< 10 kb) via an active mechanism, nonspecific to DNA sequence [25, 26]. It was shown that foreign genetic material, namely *gfp* gene, constituting part of the construct based on the maize mitochondrial plasmid and controlled by mitochondrial regulatory sequences, could be expressed and to serve as a template for DNA synthesis. The presence of the mitochondrial regulatory sequences in the construct was critical both for DNA and for RNA synthesis.

In study [60], authors obtained proofs of imported foreign DNA integration into potato mitochondrial genome via mechanism of homologous recombination. It was established that (1) the gene-reporter can be integrated into mitochondrial genome without duplications and deletions; (2) recombination occurs at regions, flanking the gene-reporter, homologous to mitochondrial genome; (3) the exchange of homologous sequences takes place at the range of 0.5-0.6 kb in regions flanking the gene reporter; (4) recombination process does not require strict homology between the integrated sequence and the mitochondrial DNA. In studies [61, 62] it was also shown that the imported DNA could serve as a

Plant mitochondrial plasmids

Plant species	Size, kb	Structure	Integration into mt-genome	References
Beta vulgaris	1.3; 1.4; 1.44; 1.6	Circular	N/a*	[33]
var. *maritima*	10.4	Linear	+ (?)	[34]
Chenopodium album L.	1.3	Circular	N/a	[35]
Brassica campestris	11.3	Linear	+ (partially)	[36]
Brassica napus, Brassica rapa	11.6	Linear	–	[37]
Daucus carota (free and integrated)	9.2	Linear	+	[38]
Gissipium	2.4; 6.5	Circular	N/a	[39]
Heliantus annuus	1.4; 1.8; 1.8	Circular	–	[40]
Lupinus albus	1.4; 1.2	Circular	–	[41]
Oenothera berteriana	6.3–13.5	Circular	N/a	[42]
Oriza sativa	0.97; 1.5; 1.55; 2.14	Circular	–	[43]
Phoenix dactylifera L.	1.16; 1.35	Circular	N/a	[44]
Sorghum bicolor	1.36; 1.7; 2.3	Circular	–	[45]
	5.3; 5.7	Linear	–	[46]
Triticum aestivum	0.3–6.0	Circular	N/a	[42]
Triticum compactum	0.3–6.0	Circular	N/a	
Vicia faba	1.48; 1.7; 1.7	Circular	N/a	[47]
Zea mays				
S-cytoplasm (free integrated)	6.4; 5.45	Linear	+	[48–50]
RU-cytoplasm (free)	7.46; 5.45	Linear	+	[51, 52]
N-cytoplasm (integrated)	2.1; 2.3	Linear	–	[53, 54]
N-cytoplasm (integrated)	1.4; 1.9	Circular	N/a	[55]
Zea diploperennis	5.4; 7.4	Linear	N/a	[56]
Zea luxurians	0.75; 5.4	Linear	N/a	[57]

*N/a – not available.

template for repair system in mitochondria isolated both from plants and mammals.

The mechanisms of the DNA import into mitochondria isolated from plants and mammals apparently are differing. For the import of DNA into plant mitochondria it was shown the participation of two mitochondrial membrane proteins, mitochondrial porin (or VDAC, voltage dependent anion channel) in the outer membrane and adenine nucleotide translocase (ANT) in the inner membrane [25]. The functionality of VDAC in DNA import was confirmed as well for the mitochondria of mammals [26] and yeast [63] but, at the same time, the inhibitors and the effectors of the ANT did not influence the process of DNA transfer in the mitochondria of these organisms. So, the DNA transport into mammalian mitochondria is more similar with that of existing in yeast rather than in plants.

In previous studies, where DNA molecules of sizes less than 10 kb (the main substrate was the mitochondrial plasmid of 2.3 kb from *Zea mays* [54]) were used as import substrates, it was shown that the import into mitochondria isolated both from plants and mammals has no specificity concerning the DNA sequence [25, 26]. For plant mitochondria it was established that (1) DNA import does not depend on nucleotide sequence of the imported molecule; (2) the import efficiency decreases with increasing of imported DNA molecule size; (3) import of circular DNA molecules is not as effec-

tive as that of linear molecules; (4) single-stranded DNA is not imported into mitochondria. For the DNA transport into mammalian mitochondria it was shown one discrepancy as compared to the import into plant mitochondria: they could uptake both the double-stranded and the single-stranded DNA. In further study [64] it was established that the DNA import into plant mitochondria is specific with respect to large DNA substrates. For DNA import into plant mitochondria and into mitochondria of human cell culture authors used the linear plasmid from rapeseed mitochondria (*Brassica napus* L.) with the size 11.6 kb [37]. This plasmid, like the 2.3 kb plasmid from *Zea mays* [54] is characterized by the terminal inverted repeats present at the each end of the molecules. It's known that inside the organelles these repeats are covalently bound to proteins involved in replication and maintaining of the plasmids. It was shown that (1) the efficiency of large DNA molecules import into plant mitochondria depends on molecule sequence; (2) the specificity of DNA import is mediated by the presence of certain elements in their sequence, namely, the terminal inverted repeats at the 5' and 3' end of the molecules. At that, the DNA import efficiency into mammalian mitochondria did depend neither on the DNA molecule sequence, nor on its size.

All those data allows presuming that (1) the DNA import into mitochondria of various taxonomic groups (plants, fungi, mammals) occurs through different mechanisms; (2) the DNA import into plant mitochondria, being specific with respect to substrate sequence and size, might take place via different biochemical mechanisms. Circular and especially linear plasmids present in mitochondria of many plant species could be a convenient tool to investigate the mechanisms of mitochondrial membrane DNA transfer and serve as mitochondrial integrative vectors.

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Генетична трансформація мітохондрій: методичний вибір між класичними біотехнологічними підходами та природною компетенцією органел

Резюме

Незважаючи на досить переконливі докази існування горизонтального перенесення генів у рослинні мітохондрії, у цій області дослідження залишається чимало невирішених питань, зокрема, не відомий молекулярний механізм горизонтального перенесення генів в органели. На сьогодні не до кінця вивчено низку питань як трансмембранного перенесення, так і умов інтеграції гетерологічної ДНК у мітохондріальний геном виду-реципієнта. Виявлені в мітохондріях багатьох видів вищих рослин кільцеві і, особливо, лінійні плазміди, з одного боку, є зручним інструментом для вивчення механізмів трансмембранного перенесення ДНК і, з іншого, – можуть слугувати основою для конструювання мітохондріальних векторів інтегративного типу.

Ключові слова: трансформація мітохондрій, імпорт ДНК, мітохондріальні плазміди, мітохондріальна мембрана.

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Генетическая трансформация митохондрий: методический выбор между классическими биотехнологическими подходами и природной компетенцией органелл

Резюме

Несмотря на достаточно убедительные доказательства существования горизонтального переноса генов в растительные митохондрии, в этой области исследований остается много нерешенных вопросов, в частности, не известен молекулярный механизм горизонтального переноса генов в органеллы. На сегодняшний день не до конца изучены многие вопросы как трансмембранного переноса, так и условий интеграции гетерологичной ДНК в митохондриальный геном вида-реципиента. Обнаруженные в митохондриях многих видов высших растений кольцевые и, в особенности, линейные плазмиды, с одной стороны, являются удобным инструментом для изучения механизмов трансмембранного переноса ДНК и, с другой, – могут служить основой для конструирования митохондриальных векторов интегративного типа.

Ключевые слова: трансформация митохондрий, импорт ДНК, митохондриальные плазмиды, митохондриальная мембрана.

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