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Review

A reevaluation of dual-targeting of proteins to mitochondria and chloroplasts ☆

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ABSTRACT

Over 100 proteins are found in both mitochondria and chloroplasts, via a variety of processes known generally as 'dual-targeting'. Dual-targeting has attracted interest from many different research groups because of its profound implications concerning the mechanisms of protein import into these organelles and the evolution of both the protein import machinery and the targeting sequences within the imported proteins. Beyond these aspects, dual-targeting is also interesting for its implications concerning shared functions between mitochondria and chloroplasts, and especially the control of the activities of these two very different energy organelles. We discuss each of these points in the light of the latest relevant research findings and make some suggestions for where research might be most illuminating in the near future. This article is part of a Special Issue entitled: Protein Import and Quality Control in Mitochondria and Plastids.

1. Introduction

Mitochondria and chloroplasts have many parallels in their evolutionary history; both are derived from bacterial endosymbionts, both are crucial contributors to the energy metabolism of the cell, both retain their own reduced genome and some components of the gene expression machinery, and both import a large proportion (over 95%) of the proteins they need to function. During this parallel evolutionary history, the two organelles have co-existed and multiplied in the same cells for around a billion years. Given the many similar metabolic and genetic functions required in mitochondria and chloroplasts, it is not that surprising that many similar proteins are found in both organelles. In most cases, these similar proteins are paralogues encoded by different genes (e.g. the 450 pentatricopeptide repeat proteins targeted to mitochondria or chloroplasts and involved in similar post-transcriptional processes in both [1]). However, there are a steadily increasing number of examples where proteins with identical sequence are found in both organelles, clearly translated from the same gene. These instances are referred to as 'dual-targeting', a term first coined in this context by Ref. [2] to describe this phenomenon.

Dual-targeting is interesting for many different reasons, and has attracted a number of reviews over the last decade and more [3–8]. From an evolutionary point of view, the loss of previous duplicated genes to concentrate two functions in a single gene is relatively unusual, as the more common tendency is neo-specialization via gene duplications. This implies that dual-targeting may confer advantages that are not immediately apparent. Dual-targeting is also interesting from a mechanistic point of view, as the protein import machineries of mitochondria and chloroplasts arose independently, are non-homologous, and therefore would not normally be expected to recognize the same proteins [9,10]. Finally, dual-targeting is interesting for its implications concerning the control of mitochondrial and chloroplast biogenesis and function. How can the activities of the two organelles be independently controlled if many of their critical components are shared?

In this short review, we treat each of these questions in turn, and attempt to explain current thinking in this field in the light of the latest discoveries. Many questions remain, however, and we also suggest the types of experiments likely to be most informative in the near future.

2. Which proteins are dual-targeted?

Over 100 proteins have been proposed to be dual-targeted, based on individual analysis, generally by tagging with fluorescent markers such as GFP [11]. It is important to note that such experiments cannot formally prove that an identical protein is imported into both compartments, as a single DNA construct can produce 2 or more proteins of distinct sequence via alternative transcription or translation starts, or alternative splicing [8]. These can still be considered examples of functional dual-targeting [12], but if the peptide signals recognized by the import machinery vary between isoforms, then this does not pose the same mechanistic conundrum as when an identical protein is transported into both organelles. A smaller number of putatively dual-targeted examples have been investigated in more detail, using

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Table 1
Over 100 proteins have been reported to be dual-targeted to mitochondria and chloroplasts.

Accession	Description	GO biological process	Solubility	Method	Ref.
At1g13900	Purple acid phosphatase 2 (AtPAP2)	Biological process	Membrane	Fluorescent tagging/Western blotting	[40]
At5g06810	Mitochondrial transcription termination factor	Biological process	Soluble	Fluorescent tagging	[41]
At5g08710	Regulator of chromosome condensation (RCC1)	Biological process	Soluble	Fluorescent tagging	[11]
At5g16200	50 S ribosomal protein-related	Biological process	Soluble	Fluorescent tagging	[42]
At4g30490	AFG1-Like ATPase protein	Biological process	Soluble	Fluorescent tagging	[42]
At5g23060	Calcium sensing receptor (CAS)	Cellular response to calcium ion	Membrane	Fluorescent tagging	[11]
At5g26940	Mg2 + dependent DNA exonuclease (DPD1)	DNA catabolic process, exonucleolytic	Soluble	Fluorescent tagging	[43]
At5g24850	Flavin adenine dinucleotide (Cry3)	DNA repair	Soluble	Fluorescent tagging/in vitro import	[44]
At1g30680	Toprim domain containing DNA helicase	DNA replication	Soluble	Fluorescent tagging	[11]
At1g50840	DNA Polymerase gamma 2	DNA replication	Soluble	Fluorescent tagging	[45]
AB174899	DNA-directed DNA polymerase 2	DNA replication	Soluble	Fluorescent tagging	[46]
At3g10690	DNA gyrase A	DNA replication	Soluble	Fluorescent tagging	[47]
AY351386	DNA gyrase A	DNA replication	Soluble	Fluorescent tagging	[48]
AY351387	DNA gyrase B	DNA replication	Soluble	Fluorescent tagging	[48]
At3g20540	DNA Polymerase gamma 1	DNA replication	Soluble	Fluorescent tagging	[11]
AB174898	DNA-directed DNA polymerase 1	DNA replication	Soluble	Fluorescent tagging	[46]
At4g31210	DNA topoisomerase	DNA replication	Soluble	Fluorescent tagging	[11]
At5g40810	Cytochrome C1 protein	Electron transporter	Membrane	Fluorescent tagging/in vitro import	[49]
CAA44055	Cytochrome C1	Electron transporter	Membrane	Fluorescent tagging/in vitro import	[49]
At3g54660	Glutathione reductase 2 (AtGR2)	Glutathione metabolic process	Soluble	Fluorescent tagging/in vitro import	[50]
P27456	Glutathione reductase	Glutathione metabolic process	Soluble	Enzyme assay/in vitro import	[51]
At4g26500	Sulfur acceptor (AtSufE1)	Iron–sulfur cluster assembly	Soluble	Fluorescent tagging	[52]
At1g21400	Thiamin diphosphate binding fold protein	Metabolic process	Soluble	Fluorescent tagging	[42]
At5g35630	Glutamine synthetase 2 (GLN2)	Metabolic process	Soluble	Fluorescent tagging/Western blotting	[53]
Nicotiana tabacum	NADP + dependant isocitrate dehydrogenase	Metabolic process	Soluble	Fluorescent tagging	[19]
Phypa_180964	Early response to dehydration 4 homolog (ERD4)	Metabolic process	Soluble	Fluorescent tagging	[21]
Phypa_202996	Phosphatidylinositol dependent phospholipase (PLC)	Metabolic process	Soluble	Fluorescent tagging	[21]
5915312	Hexokinase 8	Metabolic process	Membrane	Fluorescent tagging	[54]
5947550	Hexokinase 3	Metabolic process	Membrane	Fluorescent tagging	[54]
5947828	Hexokinase 2	Metabolic process	Membrane	Fluorescent tagging	[54]
5917393	Hexokinase 7	Metabolic process	Membrane	Fluorescent tagging	[54]
5933371	Hexokinase 9	Metabolic process	Membrane	Fluorescent tagging	[54]
5939952	Hexokinase 10	Metabolic process	Membrane	Fluorescent tagging	[54]
5942660	Hexokinase 11	Metabolic process	Membrane	Fluorescent tagging	[54]
At1g74600	PPR protein (OTP87)	mRNA modification	Soluble	Fluorescent tagging	[55]
At4g21170	PPR protein	mRNA modification	Soluble	Fluorescent tagging	[41]
At4g32400	Nucleotide carrier protein (Brittle 1)	Nucleotide transport	Membrane	Fluorescent tagging	[17]
AAA33438	Brittle 1	Nucleotide transport	Membrane	Fluorescent tagging/immuno gold labeling	[17]
At3g05790	Lon protease 4 (Lon4)	Oxidation-dependent protein catabolic process	Soluble	Fluorescent tagging/Western blotting	[56]
At5g26860	Lon protease 1 (Lon1)	Oxidation-dependent protein catabolic process	Soluble	Fluorescent tagging	[57]
At4g08390	Stromal ascorbate peroxidase (sAPX)	Oxidation-reduction process	Soluble	Fluorescent tagging/in vitro import	[50]
At5g08740	NAD(P)H dehydrogenase C1 (NDC1)	Oxidation-reduction process	Membrane	Fluorescent tagging/in vitro import	[58]
At2g39290	Phosphatidylglycerolphosphate synthase 1 (PGPS1)	Phospholipid biosynthetic process	Soluble	Fluorescent tagging	[59]
At5g04140	Ferredoxin-dependent glutamate synthase (GLS1)	Photorespiration	Soluble	Fluorescent tagging	[60]
At5g38710	Methylenetetrahydrofolate reductase family protein	Proline catabolic process	Soluble	Fluorescent tagging	[42]
At5g55200	Co-chaperone grpE protein (MGE1)	Protein folding	Soluble	Fluorescent tagging	[42]
Phypa_187670	FtsZ family protein	Protein polymerization	Soluble	Fluorescent tagging	[21]
At1g49630	Zinc metalloprotease (AtPrep2)	Protein processing	Soluble	Fluorescent tagging/in vitro import	[61]
At3g16480	Mitochondrial processing peptidase alpha 2 (MPPalpha2)	Protein processing	Membrane	Fluorescent tagging/in vitro import	[62]
At3g19170	Zinc metalloprotease (AtPrep1)	Protein processing	Soluble	Fluorescent tagging/in vitro import/ Western blotting	[61]
At3g25740	Methionine aminopeptidase 1B (MAP1B)	Protein processing	Soluble	Fluorescent tagging	[63]
Os02g52420	Methionine aminopeptidase	Protein processing	Soluble	Fluorescent tagging	[31]
At4g37040	Methionine aminopeptidase 1D (MAP1D)	Protein processing	Soluble	Fluorescent tagging	[63]
At1g11870	Seryl-tRNA synthetase	Protein translation	Soluble	Fluorescent tagging/in vitro import	[64]
BG462707	Seryl-tRNA synthetase	Protein translation	Soluble	Fluorescent tagging/Western blotting	[65]
At1g48520	glutamyl-tRNA(Gln) amidotransferase subunit B	Protein translation	Soluble	In vitro import/Western blotting	[66]
At1g50200	Alanyl-tRNA synthetase	Protein translation	Soluble	Fluorescent tagging/in vitro import	[64]
At2g04842	Threonyl-tRNA synthetase	Protein translation	Soluble	In vitro import	[64]
At2g25840	Tryptophan-tRNA synthetase	Protein translation	Soluble	Fluorescent tagging	[64]
At2g31170	Cysteinyl-tRNA synthetase	Protein translation	Soluble	Fluorescent tagging	[67]
At3g02660	Tyrosine-tRNA synthetase	Protein translation	Soluble	In vitro import	[64]
Os01g31610	Tyrosine-tRNA synthetase	Protein translation	Soluble	Fluorescent tagging	[31]
At3g12370	Ribosomal protein L10	Protein translation	Soluble	Fluorescent tagging	[68]
Os05g03030	Ribosomal protein L10	Protein translation	Soluble	Fluorescent tagging	[68]
At3g13490	Lysyl-tRNA synthetase	Protein translation	Soluble	Fluorescent tagging/in vitro import/ Western blotting	[64]
At3g25660	glutamyl-tRNA(Gln) amidotransferase subunit A	Protein translation	Soluble	In vitro import/Western blotting	[66]
At3g46100	Histidyl-tRNA synthetase	Protein translation	Soluble	Fluorescent tagging	[69]