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Review

Dual targeting of mitochondrial proteins: Mechanism, regulation and function ☆

Ohad Yogev, Ophry Pines *

Department of Microbiology and Molecular Genetics, IMRIC, Faculty of Medicine, Hebrew University, Jerusalem 91120, Israel

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ABSTRACT

One solution found in evolution to increase the number of cellular functions, without increasing the number of genes, is distribution of single gene products to more than one cellular compartment. It is well documented that in eukaryotic cells, molecules of one protein can be located in several subcellular locations, a phenomenon termed dual targeting, dual localization, or dual distribution. The differently localized proteins are coined in this review "echoforms" indicating repetitious forms of the same protein (echo in Greek denotes repetition) distinctly placed in the cell. This term replaces the term to "isoproteins" or "isoenzymes" which are reserved for proteins with the same activity but different amino acid sequences. Echoforms are identical or nearly identical, even though, as referred to in this review may, in some cases, surprisingly have a totally different function in the different compartments. With regard to mitochondria, our operational definition of dual targeted proteins refers to situations in which one of the echoforms is translocated through/into a mitochondrial membrane. In this review we ask how, when and why mitochondrial proteins are dual localized in the cell. We describe mechanisms of dual targeting of proteins between mitochondria and other compartments of the eukaryotic cell. In particular, we have paid attention to situations in which dual localization is regulated in time, location or function. In addition, we have attempted to provide a broader view concerning the phenomenon of dual localization of proteins by looking at mechanisms that are beyond our simple definition of dual targeting. This article is part of a Special Issue entitled Protein translocation across or insertion into membranes.

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* Corresponding author.
E-mail address: ophryp@ekmd.huji.ac.il (O. Pines).

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1. Introduction

Eukaryotic cells are defined by the existence of subcellular compartments and organelles. This allows the partitioning of various biochemical pathways out of the cytosolic milieu into discrete organelles. For this, each cellular compartment has a specific protein content that is vital for its function. Mitochondria are such organelles, which are responsible for energy production and essential metabolic pathways in the cell, and these organelles have been implicated in other processes such as apoptosis, aging and cancer.

Sorting of proteins to a membrane-sealed organelle, such as mitochondria, involves two main steps: i) Targeting of proteins to and specific recognition by the organelle and ii) Translocation into the organelle, through or into its membranes by an import machinery. This necessitates that the protein includes targeting and translocation information within its sequence that is recognized by the organelle receptors and import machinery. In this review we intentionally do not provide an introduction to protein targeting information within substrates and protein translocation machineries within cells. These are provided by excellent accompanying reviews in this issue dealing with protein targeting and translocation in mitochondria, chloroplasts, peroxisomes and the ER.

It is well documented that in eukaryotic cells molecules of one protein can be located in several subcellular locations, a phenomenon termed dual targeting, dual localization or dual distribution. The differently localized proteins are termed isoproteins. With regard to mitochondria, our conventional definition of dual targeted proteins refers to situations in which one of the isoproteins is translocated through/into a mitochondrial membrane. Thus, dual targeted proteins are recognized by at least one organelle's receptors and translocation machineries.

Dually targeted proteins can be located in two or more compartments, immediately after translation thereby creating a steady state ratio between the different sub-populations. In recent years it has become evident that dual targeting can be regulated; induced or rebalanced in response to cellular signaling or as a response to changing extracellular conditions. Interestingly, these proteins can perform the same or distinct activities and functions in each location. Dual targeting of proteins in eukaryotic cells is a timely topic for which several excellent reviews have been published in the last decade on different aspects of this phenomenon [1–9]. In this review, we describe mechanisms of dual targeting of proteins between mitochondria and other compartments of the eukaryotic cell. We have addressed situations in which dual targeting of proteins is regulated in time, location or function; for instance, changes in targeting under specific cellular conditions, changes in the relative amounts of the isoproteins, and additional new functions performed by one of the isoproteins. Due to the large number of studies dealing with dual targeting we have chosen in each case one or two examples in order to make a point, with the understanding that this choice was oftentimes fortuitous or subjective based on our familiarity and knowledge. In some cases while the data suggests dual localization of a protein, the mechanism by which this occurs is unknown and therefore open questions linger.

The review will deal with dual targeting mechanisms of mitochondrial proteins that are based on single or multiple translation products (Table 1). In addition, we provide a broader view concerning the phenomenon of dual localization of proteins by looking at mechanisms that are beyond our simple definition of dual targeting.

Table 1
Dual targeting mechanisms of mitochondrial protein.

Dual targeting mechanism	Genes	mRNAs	Translation products	Examples in this review[a]	Illustrated in figure
Two genes encode two isoprotein: one that contains a targeting signal which the other lacks.	2	2	2	Mdh^{YM} Aconitase^{M}	1A
Two transcripts are created by alternative transcription initiation or alternative splicing, which removes a targeting signal.	1	2	2	Hts 1^{Y}, Vas 1^{Y}, Renin^{M}	1B
Translation initiation from in-frame start codons, which removes a targeting signal.	1	1	2	Mod5^{Y}, Pol gamma 2^{P}, Hcs 1^{P}	1C
An ambiguous targeting signals is recognized by two organelles.	1	1	1	TyrRS^{P}, LpSod^{P}, NADH-cytochrome b5R^{M}, Fis 1^{M}	2A
Two targeting signals on one protein target it to two organelles.	1	1	1	NAD(P)H dehydrogenase^{M}, CYP2B1^{M}	2B
Targeting sequence is inaccessible in some of the protein molecules.	1	1	1	Aky2^{Y}, Apn 1^{Y}, ERS^{Y}, CYP2B1^{M}, Cyp1A1^{M}	2C
Reverse translocation of some of the protein molecules.	1	1	1	Fumarase^{Y}, NFS1^{Y}, Aconitase^{Y}	2D
Membrane permeabilization, release or export of proteins	1	1	1	Cytochrome C^{M}, HSP60^{M}, Mortalin^{M}	2E

[a] Y, Yeast; M, Mamalian; P, Plants.

2. Dual targeting mechanisms of mitochondrial proteins

2.1. Two (or more) translation products

2.1.1. Two or more genes

The simplest and most basic mechanism for achieving dual targeting is the existence of two genes. In this case, each gene can encode a slightly different isoprotein; one that contains a targeting signal which the other lacks. This allows the creation of two translation products that are targeted to two cellular locations (Fig. 1A). Examples for this mechanism can be found in the yeast malate dehydrogenases (MDH) and alcohol dehydrogenases (ADH). *Saccharomyces cerevisiae* contains 3 highly homologous isozymes of malate dehydrogenase. All three catalyze the interconversion of malate and oxaloacetate. While sharing the same enzymatic activity, each isoenzyme is located in a separate compartment; MDH1 participates in the tricarboxylic acid cycle in mitochondria, MDH2 functions in the cytosol as part of the malate/aspartate shuttle and MDH3 catalyzes the reaction as part of the glyoxylate shunt in peroxisomes [10–13]. The same phenomenon can be found in higher eukaryotes where MDH is encoded by two genes MDHI and MDHII, located in the cytosol and mitochondria respectively [14–16].

A second example, from higher eukaryotic cells, is the protein aconitase. Two proteins are encoded by two genes *ACO1* and *ACO2*; Aco2 is a mitochondrial enzyme of the Krebs cycle and Aco1 is a cytosolic participant in cellular iron regulation. In the case of aconitase, the two isoproteins differ in their location and also in their function. While Aco2 is an enzyme that catalyzes the conversion

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