Mitochondrial Carriers

Subjects: Biochemistry & Molecular Biology
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Definition

Mitochondrial carriers play a fundamental role in cellular metabolism, connecting mitochondrial with cytosolic reactions. By transporting substrates across the inner membrane of mitochondria, they contribute to many processes that are central to cellular function. The genome of *Saccharomyces cerevisiae* encodes 35 members of the mitochondrial carrier family, most of which have been functionally characterized.

1. Introduction

Mitochondria are subcellular organelles involved in different pathways. In addition to supplying energy, mitochondria contribute to many processes that are central to cellular function and that require the exchange of metabolites between the cytosol and the mitochondrial matrix. These organelles are surrounded by a double-membrane system consisting of an outer mitochondrial membrane (OMM) that surrounds the inner membrane (IMM); the two membranes are separated by an intermembrane space. Numerous transport processes occur between the two mitochondrial membranes. The OMM contains large pores (porins), which are large enough to allow the passage of ions and molecules as large as a small protein. The IMM is highly impermeable and, therefore, is characterized by the presence of specific carrier proteins which transport metabolites inside the mitochondria. These proteins, which are encoded by nuclear DNA, play a fundamental role in cellular metabolism since they connect the intra-mitochondrial reactions with the extra-mitochondrial (cytosolic) ones.

Mitochondrial carriers are widespread in all eukaryotes and considerable research has been conducted on characterizing the members of the mitochondrial carrier family (MCF) in yeast, mammals, plant, and insects. In particular, in *Saccharomyces cerevisiae*, 35 members of the MCF have been identified and, in large part, functionally characterized (**Table 1**).

Table 1. List of mitochondrial carriers from *Saccharomyces cerevisiae*. Alternative carrier names are in brackets.

Carrier		Substrates Transported	Function/Metabolic Pathway
ADP/ATP carrier	Aac1p Aac2p Aac3p	ADP, ATP	Oxidative phosphorylation
ADP/ATP carrier (peroxisomal)	Ant1p	ATP, AMP	Lipid metabolism

Adenosine 5′-phosphosulfate carrier	Apsc1p	Adenosine 5’-phosphosulfate 3’-phospho-adenosine 5’-phosphosulfate, sulfate, and phosphate	Thermotolerance and synthesis of methionine and glutathione at elevated temperatures
ATP-Mg/phosphate carrier	Sal1p	ADP, ATP, ATP-Mg, and Pi (Ca^{2+}-stimulated)	Glucose-induced calcium signal
Aspartate/glutamate carrier	Agc1p Ymc1p Ymc2p	Aspartate, glutamate	Nitrogen metabolism and ornithine synthesis Malate-aspartate NADH shuttle
Carnitine carrier	Crc1p	Carnitine, acetyl-carnitine, and propionyl-carnitine (medium- and long-chain acyl-carnitines less efficiently)	Lipid metabolism
Citrate carrier	Ctp1p	Citrate, tricarboxylates	Lipid and glucose metabolism
Citrate/oxoglutarate carrier	Yhm2p (Coc1p)	Citrate, oxoglutarate (oxaloacetate, succinate, and fumarate less efficiently)	Increase in the NADPH reducing power in the cytosol Component of the citrate-oxoglutarate NADPH redox shuttle
Coenzyme A carrier	Leu5p	Coenzyme A	Distribution of Coenzyme A

Dicarboxylate carrier	Dic1p	Dicarboxylates (malate, succinate, or malonate), Pi, sulfate, and thiosulfate	Anaplerotic role for the Krebs cycle
FAD carrier	Flx1p	FAD	Flavin transport
GTP/GDP carrier	Ggc1p	GTP, GDP, dGTP, dGDP, and the structurally related ITP and IDP (guanosine 5′-tetraphosphate and the (deoxy)nucleoside di- and triphosphates of U and T less efficiently)	Protein synthesis and RNA synthesis
Magnesium carrier	Mme1	Magnesium	Homeostasis of magnesium
NAD^+ carrier	Ndt1p Ndt2p	NAD^+ (dAMP and dGMP, NADH, $NADP^+$, or NADPH less efficiently)	Import NAD^+ into mitochondria
Iron carrier	Mrs3p Mrs4p	Iron	Iron accumulation
Ornithine carrier	Ort1p	Ornithine/H^+ or ornithine/ornithine (arginine and lysine less efficiently)	Arginine synthesis

Oxaloacetate carrier	Oac1p	Oxaloacetate, sulfate, and a-isopropylmalate (various substrates of the dicarboxylate and oxoglutarate carriers less efficiently)	Anaplerotic role for the Krebs cycle Leucine synthesis
Oxodicarboxylate carrier	Odc1p Odc2p	Oxoadipate, oxoglutarate (dicarboxylates and malate less efficiently)	Nitrogen assimilation Malate/aspartate shuttle
Phosphate carrier	Mir1p Pic2p	Phosphate	Oxidative phosphorylation
Pyridoxal 5’-phosphate transporter	Mtm1p	Pyridoxal 5’-phosphate transporter	Pyridoxal 5’-phosphate trafficking Iron homeostasis
Pyrimidine nucleotide carrier	Pyt1p (Rim2p)	Pyrimidine (deoxy)nucleoside mono-, di- and triphosphates	mtDNA and mtRNA synthesis
S-adenosylmethionine carrier	Sam5p	S-adenosylmethionine	Biosynthesis of biotin and lipoic acid Methylation reactions of mtDNA, mtRNA, and mitochondrial proteins
Succinate/fumarate carrier	Sfc1p	Succinate, fumarate	Gluconeogenesis

Thiamine pyrophosphate carrier	Tpc1p	Thiamine pyrophosphate, thiamine monophosphate ((deoxy)nucleotides less efficiently)	Branched chain amino acids synthesis
	Ugo1p		Mitochondrial fusion
	YDL119c (Hem25)	Glicine	Heme synthesis
	YFR045w product	?	?

With a single exception, these proteins are found in the inner membranes of mitochondria. By transporting several substrates across this membrane, they are indirectly involved in many biochemical processes, such oxidative phosphorylation (OXPHOS) (**Figure 1**), the transfer of reducing equivalents (**Figure 2**), the transport of Krebs cycle intermediates (**Figure 3**), fatty acid metabolism (**Figure 4**), gluconeogenesis (**Figure 5**), and amino acid synthesis (**Figure 6**).

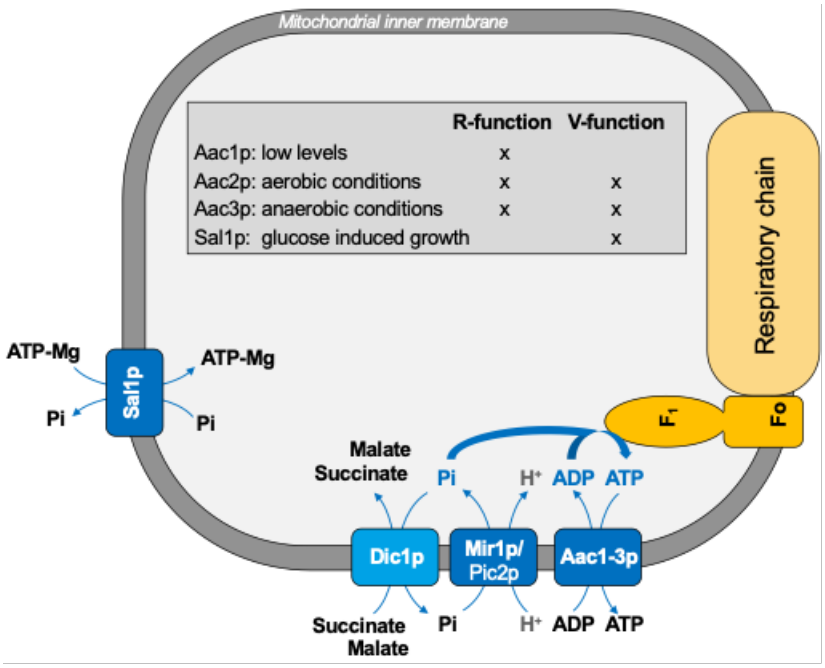

Figure 1. Transport of substrates into mitochondria for ATP synthesis. R-function (ADP/ATP exchange required for respiratory growth); V-function (ADP/ATP exchange required for viability).

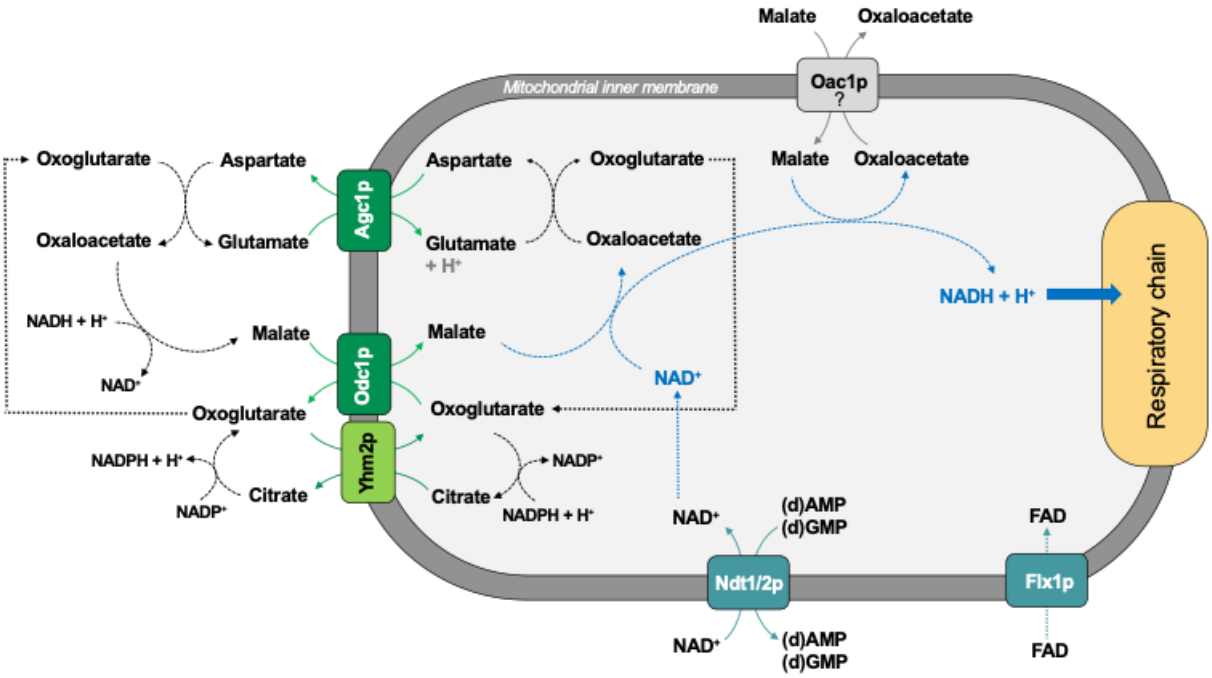

Figure 2. Transport of reducing equivalents into mitochondria.

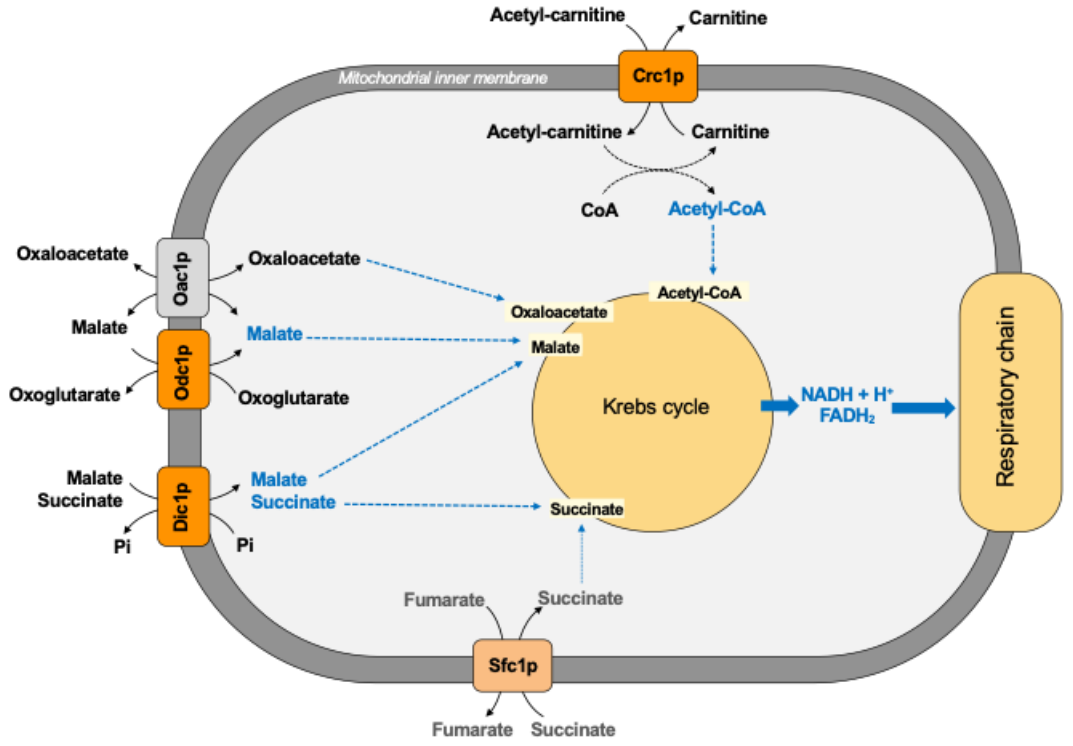

Figure 3. Mitochondrial carriers and transport of Krebs cycle intermediates.

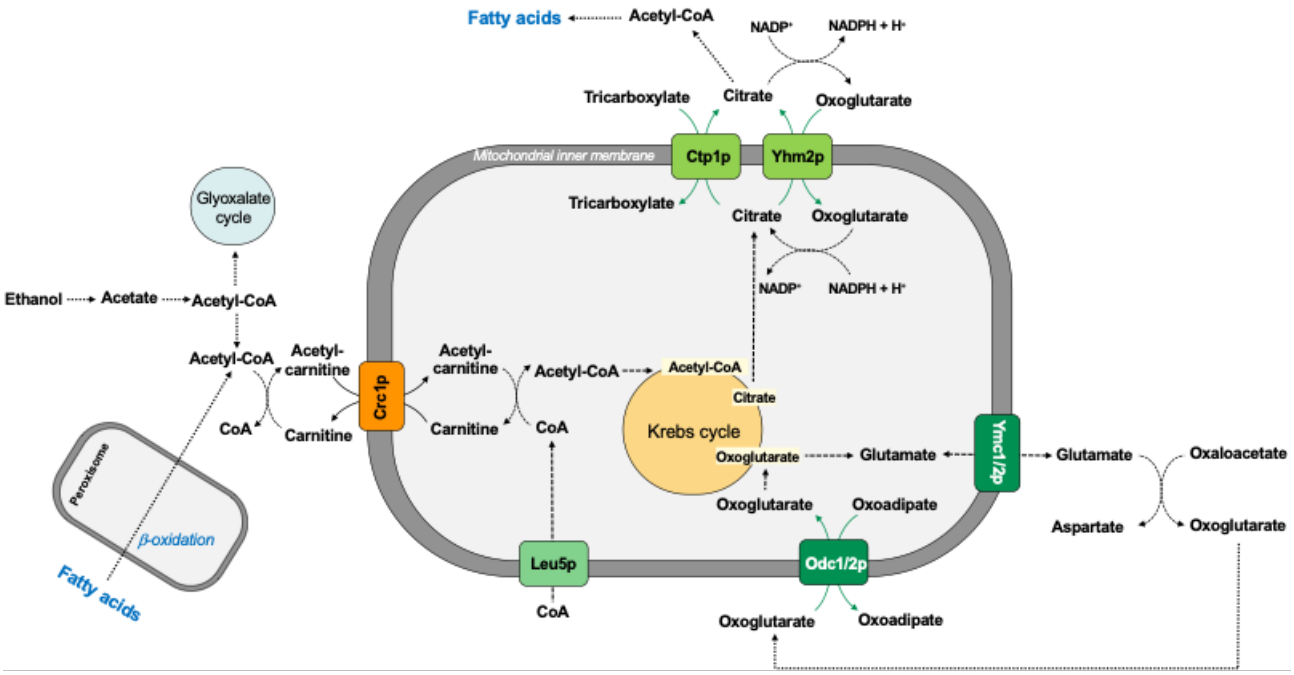

Figure 4. Mitochondrial carriers and lipid metabolism.

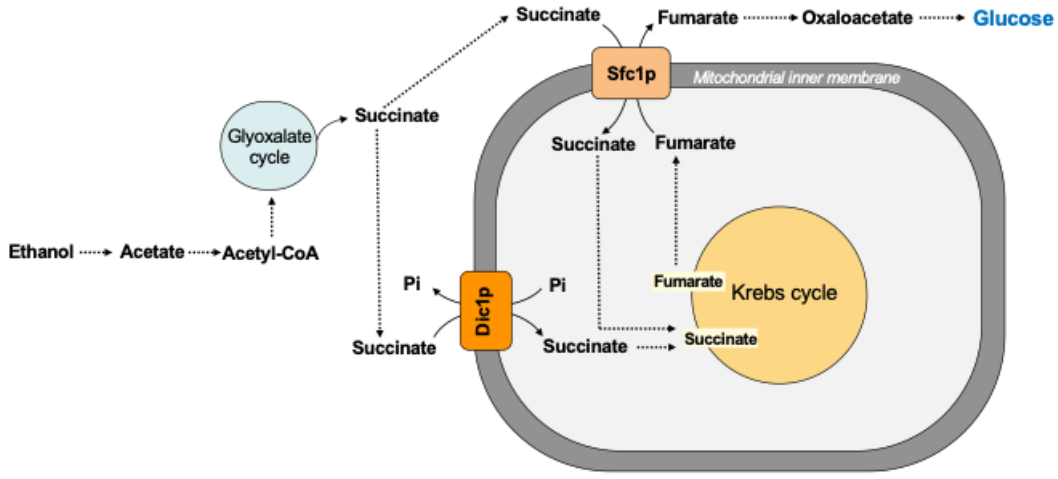

Figure 5. Mitochondrial carriers and gluconeogenesis.

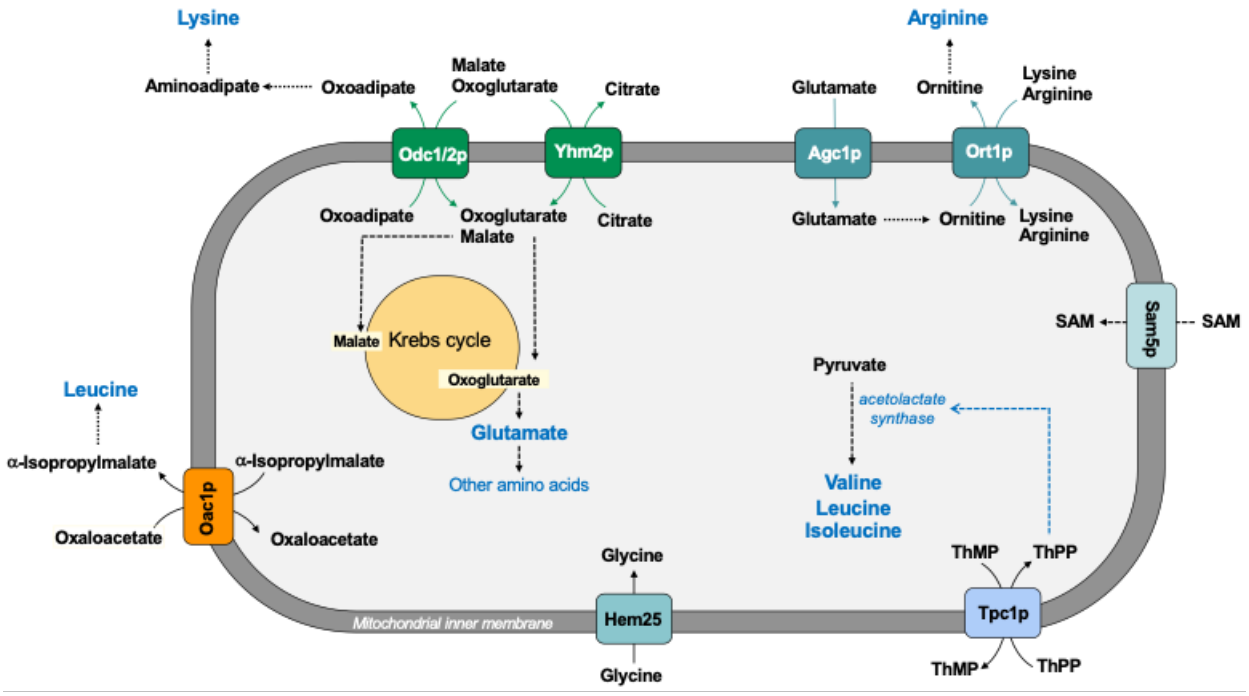

Figure 6. Mitochondrial carriers and amino acid synthesis.

2. Role and application

Despite the considerable progress made in the last years in characterizing mitochondrial carriers from *Saccharomyces cerevisiae*, many aspects related to their role in metabolic pathways connecting mitochondrial and cytosolic reactions remain to be ascertained. In fact, the function of most transport proteins has been determined by expressing the gene in *Escherichia coli* or *Saccharomyces cerevisiae,* reconstituting protein into liposomes and testing its transport activity in the presence of substrates selected on the basis of genetic, biochemical, and phylogenetic considerations.

All carrier proteins which are involved in the same metabolic pathway should be orchestrated to adequately channel substrates toward the formation of desired products. Interestingly, the same mitochondrial carrier can transport different substrates (as suggested by experiments of substrate specificity in reconstituted liposomes) depending on the metabolic pathway in which it is involved.

Taken together, all this evidence suggests that mitochondrial carriers play a key role in the adaptation of yeast metabolism in response to specific growth conditions. Their involvement in metabolic pathways can provide new insights not only on the physiological roles of mitochondrial carriers in yeast cell metabolism but also in the understanding of molecular basis of human diseases. However, many questions remain to be addressed. In fact, some carrier proteins possess specific isoforms which possess different physiological roles. At the same time, different carrier proteins can transport the same substrates depending on metabolic condition of the cell. What, when, and how much are these proteins expressed? Are these proteins distributed in the mitochondrial inner membrane, or are they localized to create specific carrier clusters associated to specific metabolic pathways? Is there a physical interaction between carrier proteins contributing to the same biochemical process? How are these proteins orchestrated to channel substrates to common pathways? These unexplored aspects are very intriguing, and more research is required to highlight new findings in the field of mitochondrial carrier biology in the yeast *Saccharomyces cerevisiae*.

Keywords

mitochondria;mitochondrial carrier;transport;metabolism