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Mitochondrial Biogenesis: Is an Old Dog Still Teaching Us New Tricks? Meeting on the Assembly of the Mitochondrial Respiratory Chain

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Meeting Report

Mitochondrial biogenesis: is an old dog still teaching us new tricks?. Meeting on the Assembly of the Mitochondrial Respiratory Chain

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The FASEB Summer Research Conference on the Assembly of the Mitochondrial Respiratory Chain took place between 5 and 10 August 2007, in Tucson, Arizona, USA, and was organized by D. Winge and E. Shoubridge.

A great loss

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Participants of this meeting were deeply saddened to learn of the passing of Ron Butow (Dallas, TX, USA), who died on 8 August 2007. Originally scheduled to present at the meeting, Butow cancelled his participation just shortly beforehand. Butow heroically battled cancer for more than 10 years and had remained an extremely active member of the mitochondrial community during this time. Butow was a giant in this field and throughout his career had used elegant genetic and biochemical approaches to study many areas of mitochondrial function, including protein import and, more recently, the organization and inheritance of the mitochondrial genome. His contributions to this field were enormous and he will be deeply missed by all in the mitochondrial and yeast genetic communities.

Introduction

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A FASEB summer research conference held in Tuscon, Arizona, USA in August 2007 focused on the broad field of mitochondrial respiratory chain complexes, their assembly and regulation. Although commonly referred to as the ‘powerhouse of the cell', mitochondria and their functions are not limited to the aerobic production of ATP. Rather, mitochondrial metabolism interfaces with many cellular metabolic processes, such as lipid metabolism—both catabolic and anabolic—FeS cluster metabolism, haem biosynthesis, programmed cell death and metal metabolism, to name but a few. As mitochondrial function and oxidative phosphorylation (OXPHOS) capacity are crucial to all eukaryotic cells, perturbations in the function of this organelle underlie many cellular metabolic disorders, and therefore give rise to various clinical disorders, from cardiac and muscle myopathies to neuromuscular defects (Shoubridge, 2001; Zeviani & Spinazzola, 2003; Fig 1). This FASEB conference saw the gathering of many scientists active in the field and whose interests ranged from basic to clinical mitochondrial biology.

Figure 1

Human oxidative phosphorylation disorders. Diseases associated with defects of the respiratory chain complexes can be due to mutations in the genes of the structural subunits of the five complexes, or to the inactivation of complex specific assembly factors. **...**

The biogenesis of mitochondria and the assembly of respiratory chain complexes have been active areas of research for the past 30–40 years. During this time, many significant advances have been made in our understanding of mitochondrial biogenesis and the crucial role that this organelle has in cellular metabolism. However, as is often—or always—the case in biological research, as one question is answered, many more emerge as we begin to appreciate the complexity of mitochondria and the many diverse cellular processes that they interface with. This issue of the complexity of discovery and the unveiling of new areas of research was a main theme that W. Neupert (Munich, Germany) covered in his opening plenary lecture. Neupert provided a historical perspective of the field of mitochondrial biogenesis as he detailed the advances made since the discovery of the mitochondrial genome and the demonstration that most mitochondrial proteins are encoded by nuclear genes and have to be imported into the organelle. As outlined by Neupert, the import of nuclear encoded proteins into the mitochondria is facilitated by protein translocases located in the outer and inner mitochondrial membranes: the TOM and TIM translocases, respectively (Bohnert *et al*, 2007; Dolezal *et al*, 2006; Neupert & Herrmann, 2007).

Protein import pathways

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The TOM and TIM machineries are multi-subunit complexes, and many of the polypeptides that comprise them have been shown to be essential in the yeast *Saccharomyces cerevisiae*, thus reflecting the importance of the protein import process for cell viability. After the yeast genome sequencing and gene deletion projects were completed, the characterization of the predicted mitochondrial proteins essential for cell viability proved to be a fruitful avenue for the identification of new components of the TOM and TIM machineries.

D. Rapaport (Tübingen, Germany) discussed the role of the sorting and assembly machinery (SAM) complex—which acts downstream of the TOM complex—in promoting the sorting and assembly of outer membrane proteins that adopt β-barrel structures. Although research in recent years has given new insights into the protein components and mechanisms that direct these β-barrel proteins into membranes, the process of insertion of tail-anchored outer membrane proteins remains elusive. Rapaport showed that mitochondrial fission 1 protein (Fis1)—a C-terminally tail-anchored model protein—can insert its tail directly into the lipid bilayer of the outer membrane without the aid of the known TOM and SAM components. Although it is still unclear which lipids promote this insertion, the finding reawakens a largely neglected area in the field: the role of lipids in the protein biogenesis pathway.

The molecular mechanism of protein translocation across the TIM23 machinery and the role of the matrix-localized mitochondrial heat shock protein 70 (mtHsp70) chaperone is an ongoing debate in the field. The ‘power-stroke' model favours an active mechanical pulling force on the precursor protein that drives the forward import step and is coupled to a conformational change of mtHsp70, which is bound to the incoming precursor. By using engineered mitochondrial precursor proteins that contain polyglycine segments of different lengths—which are considered to exclude mtHsp70 binding to the precursor—T. Endo (Nagoya, Japan) provided evidence to suggest that transport of the precursor is largely mediated not by a ‘power-stroke', but through a ‘Brownian motion' based process.

A recently discovered mitochondrial import pathway is that of intermembrane space-targeted proteins that contain intramolecular disulphide bonds (Tokatlidis, 2005; Milenkovic *et al*, 2007). As J. Herrmann (Kaiserslautern, Germany) and C. Koehler (Los Angeles, CA, USA) outlined in their talks, this import pathway has several similarities to the sulphydryl oxidase-based protein-folding pathway in the bacterial periplasm. In yeast mitochondria, this pathway involves the essential proteins Mia40 and Erv1. Mia40 acts as a cysteine platform and shuffles the formation of inter-disulphide bonds between Mia40 and the imported substrates—thus forming intermediates in the pathway of intra-disulphide bridge formation within the substrate protein—and ultimately promotes the release of correctly folded, oxidized proteins. The redox recycling of Mia40 is ensured by Erv1, a sulphydryl oxidase that reoxidizes Mia40 and makes it available for the next round of substrate import. Herrmann and Koehler also presented evidence for a role of cytochrome *c* as an electron acceptor in the Erv1-reoxidization pathway. Moreover, Koehler presented exciting physical and genetic data showing that cytochrome *c* peroxidase 1 (Ccp1) is also directly involved in Erv1 reoxidization. Therefore, these findings establish that a cross-communication exists between the activity of the Mia40/Erv1 import pathway and that of the respiratory chain complex.

Assembly of oxidative phosphorylation complexes

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The process of OXPHOS depends on the presence of functional multi-subunit respiratory chain complexes embedded in the mitochondrial inner membrane. These complexes need to be assembled from their individual subunits, which are either synthesized in mitochondria or imported from the cytosol. Moreover, the OXPHOS complexes need to be equipped with cofactors such as copper, haem or FeS clusters that are necessary for their electron transport capacity. In addition to the protein translocases described above, a whole range of complex-specific chaperones, assembly factors and enzymes involved in the biosynthesis and incorporation of prosthetic groups are necessary for the assembly of intact and enzymatically competent complexes. The analysis of the molecular mechanisms that underlie the various steps of these assembly processes represented the heart of the meeting.

The synthesis of the mitochondrially encoded proteins represents an important early step in the biogenesis of many of the OXPHOS complexes. G. Shadel (Yale, CT, USA) reported that mitochondrial ribosomal protein L7/L12 (Mrpl12) can be found in direct physical association with the mtRNA polymerase, and that purified recombinant Mrpl12 protein could stimulate the transcription of mitochondrially encoded genes in a cell-free mitochondrial transcription assay. Shadel speculated that the interaction of this ribosomal subunit with the mtRNA polymerase might represent a new regulatory mechanism that acts to ensure coordination between mitochondrial transcription and ribosome assembly and/or translational capacity, and thereby to control mitochondrial gene expression.

To adapt mitochondrial functions to cellular demands, nuclear genes that encode mitochondrial proteins are tightly regulated. Z. Arany (Boston, MA, USA) reported on the crucial role of the transcription factor peroxisome proliferator-activated receptor-γ, coactivator 1-α (PGC1α) for the regulation of mitochondrial biogenesis in skeletal muscle. The expression of Pgc1α is stimulated by exercise, where it exerts many effects on both mitochondrial levels and function. In addition to increasing mitochondrial abundance and vasculogenesis, elevated expression of Pgc1α has been shown to protect muscles from atrophy, such as that caused by denervation of the muscle. Arany speculated that drugs that increase Pgc1α expression or activate the general promotion of mitochondrial function through Pgc1α could eventually lead to a therapeutic strategy against muscle diseases.

A further level of coordination of mitochondrial synthesis and assembly of respiratory chain complexes is beautifully illustrated in the assembly pathway of the cytochrome oxidase complex (COX; complex IV) of the OXPHOS system. The crucial catalytic and core subunits—Cox1, Cox2 and Cox3—are mitochondrially encoded. Both T. Fox (Ithaca, NY, USA) and A. Barrientos (Miami, FL, USA) discussed the intricate feedback system used in yeast mitochondria to balance the level of synthesis of the Cox1 protein with the assembly of the COX complex. This system involves a dual-function protein termed Mss51, which binds to both Cox1 mRNA to promote Cox1 translation and to the newly synthesized, unassembled Cox1 polypeptide. The latter step requires the presence of the Cox14 protein. Mss51 remains bound to the Cox1 polypeptide until Cox1 proceeds with its assembly pathway, a step that results in the release and recycling of Mss51. If the further assembly of Cox1 is hindered, Mss51 remains bound to the unassembled Cox1 protein and therefore becomes a limiting factor for the next round of Cox1 mRNA translation. This elaborate feedback pathway acts to coordinate the levels of protein produced with the assembly of active enzyme complexes. Barrientos also reported that the subsequent assembly of Cox1—which results in the release of Mss51—is promoted through the action of the Shy1 protein. Shy1 is the yeast orthologue of human SURF1, a protein associated with Leigh syndrome—a severe neurological disorder of infancy that is commonly associated with a systemic COX deficiency.

As indicated above for Shy1/Surf1 and its link to Leigh syndrome, defects in OXPHOS biogenesis and function are the underlying cause for various human neuromuscular defects or syndromes. However, the most common diseases associated with OXPHOS metabolism (approximately 40%) can be attributed to defects within complex I, the NADH dehydrogenase complex. M. Ryan (Melbourne, Australia) described the analysis of a complex I assembly defect in mitochondria isolated from the fibroblasts of a patient suffering from a cardioencephalomyopathy caused by mutations in the gene encoding the complex I intermediate associated protein of 30 kDa (CIA30) protein. Ryan showed that CIA30 interacts directly with assembly intermediates of complex I. Introduction of wild type CIA30 into the patient's fibroblasts restored the normal assembly of an enzymatically active complex I in these cells. Therefore, CIA30 is a crucial component in the early assembly steps of complex I, and defects in this protein can cause mitochondrial disease.

The meeting also presented a forum for young researchers selected from the poster presentations to talk about their exciting new data. Two of these speakers, D. Mick (Freiburg, Germany) and F. Pierrel (Salt Lake City, UT, USA) identified two new components—termed cytochrome *c* oxidase assembly factor (Coa)1 and Coa2—involved in the assembly of the COX complex, using biochemical or genetic approaches. Although Coa1 seems to have a role in the early steps of Cox1 assembly together with Mss51, Cox14 and Shy1, the molecular role of Coa2 is still unknown.

The assembly of the yeast cytochrome bc_1 complex—complex III of OXPHOS system—was the subject of a talk by V. Zara (Lecce, Italy). By using native gel electrophoresis and yeast mutants deficient in specific nuclear-encoded subunits of the cytochrome bc_1 complex, Zara presented evidence for the formation of specific subcomplexes—assembly intermediates that formed and can be used to define the multi-step assembly pathway of this multi-subunit enzyme. S. Ackerman (Detroit, MI, USA)

discussed the assembly of complex V, the F_1F_o-ATP synthase enzyme. Ackerman focused on the chaperones Atp11 and Atp12 required for facilitating the co-assembly of F_1-subunits α and β, respectively, which co-assemble with a $\alpha_3\beta_3$ stoichiometry. High-resolution crystal structures of both Atp11 and Atp12 were presented that will be invaluable for future studies of the mechanism of action of these important chaperones.

Cofactor biosynthesis and incorporation

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Mitochondria are essential in eukaryotic cells. Not only are the components of the mitochondrial transport machineries and chaperones involved in protein folding essential, but also the proteins participate in the biosynthesis of FeS clusters (Lill & Mühlenhoff, 2006). In fact, mitochondria and their FeS cluster assembly machinery are indispensable for life owing to their function in the maturation of all cellular FeS proteins. One such essential extra-mitochondrial FeS cluster-containing protein is Rli1, which participates in the biogenesis of cytosolic ribosomes. A focus of current research is on unravelling of the role of mitochondria in cytosolic FeS protein biogenesis. R. Lill (Marburg, Germany) introduced a reconstituted assay system—using isolated mitochondria and components of the cytosolic CIA machinery—which allows the *in vitro* study of this maturation process. This system is an essential step for further analyses on the mechanisms by which cytosolic FeS proteins are generated.

P. Cobine (Salt Lake City, UT, USA) addressed the issue of copper transport into mitochondria. He showed that a pool of copper accessible to proteins exists in the mitochondrial matrix. An uncharacterized small molecule seems to act as the copper-binding factor; this factor is also present in the cytosol, but apparently only as an apo-form. The data suggest that this molecule is involved in copper transport between the cytosol and the mitochondrial matrix. It is crucial to identify this factor to gain insight into the molecular mechanisms of copper homeostasis. S. Merchant (Los Angeles, CA, USA) discussed that *Chlamydomonas* chloroplasts seem to have a salvage pathway for copper, indicating that copper is recycled for use in other locations of the cell. When grown under copper-limiting conditions, a haem-containing cytochrome c_6 protein functionally replaces the copper-containing plastocyanin protein of chloroplasts. Merchant explained that there seems to be a hierarchy of copper allocation within cells in which the mitochondrial COX complex has the highest priority over the available copper. In times when copper is limiting, the existing plastocyanin is proteolytically degraded, thus freeing the copper, which is then available for recycling to the mitochondrion.

Oxidative phosphorylation supercomplexes

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OXPHOS complexes do not exist as physically separate entities within the inner mitochondrial membrane but rather co-assemble into higher-ordered structures referred to as ‘supercomplexes' (Schägger & Pfeiffer, 2000). J. Vonck (Frankfurt, Germany) presented an interesting EM-based single particle analysis of the supercomplex composed of complexes I, III and IV from bovine heart mitochondria. This type of approach is invaluable to our understanding of the assembly and organization of the supercomplexes. R. Stuart (Milwaukee, WI, USA) discussed how the organizational state of OXPHOS supercomplexes—in particular that of the ATP synthase—has a direct role in establishing the normal architecture of the inner membrane cristae. Stuart presented evidence that the organizational state of the ATP synthase complex also influences the organization of the complex III–IV supercomplex, thus suggesting that OXPHOS complexes might be coorganized into local areas or platforms within the cristae membrane. In addition, P. Rehling (Göttingen, Germany) presented evidence for the presence of different forms of the complex III–IV supercomplex within one mitochondrial system. Rehling showed that the III–IV supercomplex associates with the Tim21-containing TIM23 complex and also with Shy1, Cox14 and Mss51—components involved in the assembly of the COX complex. The intriguing finding that a population of TIM23 machinery associates with the respiratory chain complexes raises many new questions. Rehling speculated that this association might be bioenergetically favourable for the activity of the TIM23 machinery. Alternatively, this association might have a role in the sorting of populations of the TIM23 machinery to different environments in the inner membrane, for example either to the inner boundary membrane—that is, to the inner membrane closely opposed to the outer membrane—or to the cristae membrane. Neupert and A. Reichert (Munich, Germany) used an immuno-electron microscopy-based approach to argue in favour of a dynamic sublocalization of the TIM23 machinery within the inner membrane.

Mitochondrial structure and inheritance

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The schoolbook picture of mitochondria as static, kidney-like shaped organelles has been found to be far from reality. In fact, today we know that mitochondria are highly dynamic organelles that undergo constant fission and fusion events, and networks within the cell (Hoppins *et al*, 2007; Okamoto & Shaw, 2005). Mitochondrial fusion and fission require conserved protein machineries at the outer and inner membranes that mediate membrane mixing and division events (Fig 2). GTPases of the dynamin family have a crucial role in both processes. The GTPase Dnm1/Drp1 acts as a central component for the division of the outer membrane. J. Nunnari (Davis, CA, USA) showed that the self-assembly of Dnm1 into oligomers promotes mitochondrial membrane constriction and scission. Interestingly, a chemical genetics screen performed by the Nunnari laboratory led to the identification of a

quinazolinone derivative that specifically blocks the polymerization of Dnm1 and, concomitantly, mitochondrial division. While this new tool allows researchers to manipulate Dnm1 functionality experimentally, it blocks Dnm1-mediated division in mammalian cells and mitochondrial outer membrane permeabilization during apoptosis, indicating that Dnm1 functions as an integrator of cellular physiology. H. McBride (Ottawa, Canada) showed that reversible SUMO modification controls the function of Dnm1 in mammalian cells. The newly identified SUMO E3 ligase of the outer membrane, MAPL, seems to have a crucial role in Drp1-dependent mitochondrial fragmentation and, thus, in the regulation of mitochondrial dynamics. S. Hoppins (Davis, CA, USA) presented an exciting new study of the outer membrane protein Ugo1, which is required for mitochondrial fusion. Hoppins described the isolation and characterization of two distinct classes of *ugo1* alleles, one class that is defective in outer membrane fusion and a second class that is solely defective in inner membrane fusion. Thus, Ugo1 appears to be directly involved in the coordination of both outer and inner membrane fusion. Hoppins also postulated that Ugo1 acts as an adaptor protein to promote the assembly of fusion competent machines in both the outer and inner mitochondrial membranes.

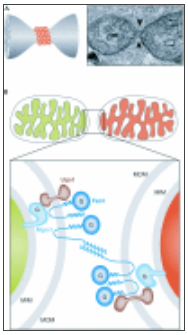

Figure 2

Mechanisms of mitochondrial fission and fusion. (**A**) A model of the mechanism of mitochondrial fission, in which the construction of membranes is driven by the assembly of Dnm1 (represented by red spheres) onto the mitochondrial surface (left). Thin section **...**

Similar to Dnm1, Mgm1/OPA1 (OPA1 for optic atrophy 1) is a GTPase and member of the dynamin protein family. OPA1 is the human homologue of the yeast Mgm1, and both regulate the morphology of the inner mitochondrial membrane. The function of OPA1 is controlled through selective proteolytic processing, and different proteases have been suggested to contribute to the maturation events. A. Reichert (Munich, Germany) discussed the analysis of reconstituted Mgm1 processing in yeast mitochondria and provided evidence that, in this system, Mgm1 is not processed by the rhomboid protease PARL or its yeast homologue Pcp1, but rather by the m-AAA protease complex of the inner membrane. In addition, studies of Opa1 processing presented by D. Chan (Pasadena, CA, USA) showed that, in mammalian cells, the i-AAA protease also contributes to Opa1 maturation by cleaving the so-called S2 site. Thus, it seems that many distinct proteolytic events might contribute to Opa1 maturation and that its regulation could be achieved through different pathways. Along this central theme, a new component in the processing of OPA1/Mgm1 was introduced by T. Langer (Cologne, Germany). Mitochondrial prohibitins have been implicated in a wide range of cellular functions. Langer showed that prohibitin 2 (Phb2) has a crucial role in the processing of Opa1 in murine mitochondria. Phb2 knockout cells display severe morphological defects and are affected in cell proliferation. At the molecular level, they show aberrant processing of Opa1 and the selective loss of the L-Opa1 isoform. Introduction of the L-Opa1 isoform in Phb2$^{-/-}$ cells could partly rescue this morphological defect. These analyses indicate that a crucial cellular function of prohibitins is to control processing of Opa1.

New directions in mitochondrial research

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Mitochondria turned out to be an attractive target for proteomic analyses, which led to the identification of new mitochondrial proteins and concomitantly to the discovery of new import pathways. As C. Meisinger (Freiburg, Germany) described, attention has now turned to more specialized questions that can be answered on a proteomic scale, such as the post-translational modification status of mitochondrial proteins. Such analyses will be invaluable to learn more about how mitochondrial function is regulated at the molecular level and also how this regulation is linked to the signals from outside of mitochondria. Another potentially exciting avenue of mitochondrial research was presented by L. Scorrano (Padova, Italy; Geneva, Switzerland), who discussed the physical relationship between the mitochondria and the endoplasmic reticulum membrane system. Scorrano presented evidence for the role of one of the two mitofusin (Mfn) proteins, Mfn2, in tethering mitochondrial membranes to regions of the endoplasmic reticulum. Areas of direct contact between the endoplasmic reticulum and mitochondria might have an important role in mitochondrial Ca^{2+} uptake from the ER or in lipid transfer between the different membrane systems.

It is clear that regulated protein maturation by the mitochondrial rhomboid proteases PARL/Pcp1 is important for the function of the mitochondrial morphology proteins OPA1/Mgm1 and identifying new targets of these mitochondrial proteases now represents an active area of research. Flies bearing defects in the Parkinson-related protein kinase *PINK1* exhibit mitochondrial dysfunction and show loss of dopamine neurons—a type of neuron known to degenerate in Parkinson disease. By using *Drosophila* as a model system, A. McQuibban (Toronto, Canada) showed a role of the mitochondrial protease rhomboid-7 in the maturation of Pink1.

This finding underscores the growing complexity of intramitochondrial protein modification processes, how they affect cellular function and the fact that disturbances in these processes might lead to severe clinical disorders.

A technical advance that will surely boost analysis of mitochondrial dynamics are the new high-resolution fluorescence microscopic techniques as discussed by S. Jakobs (Göttingen, Germany). He showed that the use of high-resolution light microscopy now allows the visualization of membrane contact sites within mitochondria, of which HeLa cells contain approximately 200 μm^{-2}, and to gather information about the dynamic distribution of protein complexes. In addition to the technical advances now introduced into the field, many unexpected observations presented at the meeting will surely lead into new routes of mitochondrial research. One such observation was presented by V. Soubannier (Ottawa, Canada) who showed that mitochondria bud off different kinds of vesicles of 70–120 nm in diameter that are surrounded by single or double membranes. The formation of mitochondria-derived vesicles was shown to be independent of Drp1 function and could be reconstituted *in vitro*, where the presence of cytosol appears to be a limiting factor for the budding reaction. It will be exciting to analyse the fate of these vesicles and to learn how their formation is regulated.

Rosemary A. Stuart

Peter Rehling

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This article is dedicated to R. Butow, a pioneer of mitochondrial research who will be greatly missed in the field. We thank our colleagues for the great discussion and for sharing their newest research findings with us. We apologize to all those participants who gave excellent presentations that could not be mentioned in this report and to those whose work could not be cited owing to space limitations.

References

Go to:

Bohnert M, Pfanner N, van der Laan M (2007) A dynamic machinery for import of mitochondrial precursor proteins. FEBS Lett 581: 2802–2810 [PubMed]

Dolezal P, Likic V, Tachezy J, Lithgow T (2006) Evolution of the molecular machines for protein import into mitochondria. Science 313: 314–318 [PubMed]

Hoppins S, Lackner L, Nunnari J (2007) The machines that divide and fuse mitochondria. Annu Rev Biochem 76: 751–780 [PubMed]

Lill R, Mühlenhoff U (2006) Iron-sulfur protein biogenesis in eukaryotes: components and mechanisms. Annu Rev Cell Dev Biol 22: 457–486 [PubMed]

Milenkovic D, Müller J, Stojanovski D, Pfanner N, Chacinska A (2007) Diverse mechanisms and machineries for import of mitochondrial proteins. Biol Chem 388: 891–897 [PubMed]

Neupert W, Herrmann JM (2007) Translocation of proteins into mitochondria. Annu Rev Cell Dev Biol 76: 723–749 [PubMed]

Okamoto K, Shaw JM (2005) Mitochondrial morphology and dynamics in yeast and multicellular eukaryotes. Annu Rev Genet 39: 503–536 [PubMed]

Schägger H, Pfeiffer K (2000) Supercomplexes in the respiratory chains of yeast and mammalian mitochondria. EMBO J 19: 1777–1783 [PMC free article] [PubMed]

Shoubridge EA (2001) Cytochrome *c* oxidase deficiency. Am J Med Genet 106: 46–52 [PubMed]

Tokatlidis K (2005) A disulfide relay system in mitochondria. Cell 121: 965–967 [PubMed]
Zeviani M, Spinazzola A (2003) Mitochondrial disorders. Curr Neurol Neurosci Rep 3: 423–432 [PubMed]