99% of all mitochondrial proteins are synthesized in the cytosol from where they are imported into mitochondria. In contrast to matrix proteins, many proteins of the intermembrane space (IMS) lack presequences and are imported in an oxidation-driven reaction by the mitochondrial disulfide relay. Incoming polypeptides are recognized and oxidized by the IMS-located receptor Mia40. Reoxidation of Mia40 is facilitated by the sulfhydryl oxidase Erv1 and the respiratory chain. The mitochondrial disulfide relay - though structurally unrelated - functionally resembles the Dsb (disulfide bond) system of the bacterial periplasm, the compartment from which the IMS was derived two billion years ago.

Mitochondria consist of two aqueous compartments, the matrix and the IMS. The mitochondrial genome codes only for roughly a dozen different proteins and the vast majority of mitochondrial proteins is nuclear encoded. Even simple organisms like baker’s yeast contain several hundred matrix proteins. Matrix proteins are synthesized in the cytosol as precursors with N-terminal presequences (also referred to as matrix-targeting signals) which are processed following translocation. The import of matrix-destined preproteins is mediated by translocases in the outer membrane (TOM complex) and the inner membrane (TIM23 complex) in an ATP- and membrane potential-dependent process (for review see (1-3)). Proteomic studies suggest that positively charged presequences are consistently found on all matrix proteins although in some cases they are not proteolytically removed (4,5).

So far about 50 different proteins were identified in the IMS of yeast mitochondria and the list of IMS proteins is rapidly growing (6). The functions of these proteins are diverse. In addition to components involved in mitochondrial respiration, the IMS contains many proteins which transport proteins, metabolites, lipids or metal ions between both mitochondrial membranes. In addition, several proapoptotic components are stored in the IMS and released when the cell death program is triggered (7).

Some IMS proteins are synthesized in the cytosol as preproteins carrying bipartite presequences which consist of a matrix-targeting signal followed by a hydrophobic sorting region. The latter serves as a stop-transfer sequence that is inserted into the inner membrane during protein import and removed by IMS-located proteases (8). Proteins with bipartite presequences embark on the general matrix-directed protein targeting pathway from which they are redirected into the IMS. However, many, if not most IMS proteins lack N-terminal targeting signals and are sorted into the IMS on a unique import route that differs in many respects from the matrix-targeting pathway. Import of many of these proteins relies on the mitochondrial disulfide relay which will be introduced in the following.

The mitochondrial disulfide relay: Mia40 and Erv1

The IMS proteins Mia40 and Erv1 represent the central components of the disulfide relay system. Both proteins are ubiquitously present in eukaryotes and highly conserved. They are essential for viability in yeast and conditional mutants show severe defects in the biogenesis of mitochondria and - presumably as secondary effects - in other cellular activities (9-14).

The oxidoreductase Mia40

Mia40 binds directly to imported IMS proteins and therefore might serve as intramitochondrial import receptor. Mia40 comprises a highly conserved domain of about 8 kDa. The structures of this domain of the human and yeast Mia40 proteins were recently
solved by NMR and crystallography (15-17). This domain contains six invariant cysteine residues: A redox-active CPC motif (-290 mV) is followed by a twin CX$_2$C motif (see below) that forms two structural disulfides (Fig. 1A). The CPC motif is part of a short helix that is connected via a flexible region to a rigid helix-loop-helix region that is stabilized by the twin CX$_2$C motif. The two helices form a hydrophobic binding groove that is positioned in close proximity to the redox-active disulfide bond. This groove serves as binding region for substrates which are presumably recognized by so-called MISS (for mitochondrial intermembrane space targeting signal) (18,19).

In fungi, but not in animals and plants, Mia40 proteins contain N-terminal linker regions that anchor them in the inner membrane (13,14). In yeast, the N-terminal anchor region is not essential (13) and their function is less clear. It is conceivable that the addition of a bipartite import signal might be advantageous under anaerobic conditions when the oxidation-driven import via the mitochondrial disulfide relay pathway might be less efficient.

The oligomeric state of Mia40 is not known. On blue native gels, yeast Mia40 migrates at 150-180 kDa (12) from which it was suggested that Mia40 is part of a larger complex. Alternatively, Mia40 might migrate exceptionally slow on these gels; indeed already on denaturing SDS-PAGE the 40 kDa protein migrates at about 60 to 70 kDa (12,13). The recombinant expression of the conserved domain of Mia40 did not reveal any evidence for dimer or oligomer formation.

**The sulfhydryl oxidase Erv1**

The second component of the disulfide relay, Erv1, was initially identified as a component that can stimulate liver regeneration (20). In these experiments, parts of the liver of rats were removed and factors of liver extracts were identified which improved regeneration of the organ. Rat Erv1 was found to serve as growth factor for liver regeneration and, in mammals, Erv1 is therefore also referred to as augmenter of liver regeneration (ALR), growth factor erv1-like (GFER), or hepatopoietin. Whether Erv1 plays indeed a physiological role in liver development is not known.

Erv1 consists of two domains, an N-terminal less structured region (shuttle domain) and a C-terminal FAD-binding domain (10,21,22) (Fig. 1B). Several structures of the FAD-binding domain of yeast and human Erv1 were solved by NMR and crystallization revealing a conserved four-bundle structure holding the FAD factor non-covalently bound in a hydrophobic, deeply embedded pocket (15,16,23-26). A surface-exposed CXXC motif is located in proximity to the isoalloxazine ring of the FAD which is efficiently oxidized by electron transfer to the FAD. A second redox-active CXXC motif is part of the flexible N-terminal domain of Erv1. Erv1 forms a dimer in which the cysteine pairs of one N and one FAD domain from two opposing subunits are in close proximity allowing an efficient intermolecular oxidation of the N-terminal CXXC motif (27-30). The N-terminal region serves as shuttle domain that interacts with Mia40 (see below).

The FAD domains in some Erv1 proteins (for example the Arabidopsis thaliana homolog) contain a short but well defined hydrophobic tunnel through which oxygen has access to the N5 nitrogen of the FAD isoalloxazine ring system (21,25). Thereby oxygen can directly oxidize the FAD moiety which leads to the production of hydrogen peroxide. Mammalian Erv1 proteins lack this hydrophobic tunnel, presumably to prevent hydrogen peroxide formation. In fungi, and most likely also in metazoans, FAD oxidation is mediated by cytochrome c, a highly abundant component in the IMS. In vitro, collision of reduced Erv1 with oxidized cytochrome c allows rapid electron exchange (31-33). At least in yeast, cytochrome c is presumably the predominant oxidant of Erv1 since mutants lacking cytochrome c or cytochrome c oxidase accumulate Mia40 in its reduced form. Thus, electrons from the disulfide relay pathway are channeled into the respiratory chain and presumably contribute to the formation of the mitochondrial membrane potential and ATP production. However, in comparison to the electrons originating from NADH and FADH$_2$, their contribution is very minor.

Yeast cells can grow anaerobically. It is not clear how Erv1 oxidation is achieved in the absence of oxygen. Interestingly, it was reported that cytochrome c becomes essential upon oxygen depletion (34). This suggests that cytochrome c is required for Erv1 oxidation.
under these conditions but it remains unclear how cytochrome c is oxidized anaerobically.

The metal-binding protein Hot13

Hot13 is a small cysteine-rich IMS protein that improves the performance of the disulfide relay to some degree (35). In contrast to Mia40 and Erv1, Hot13 is dispensable in yeast and Hot13-deficient cells show no obvious defects. In vitro experiments suggest that Hot13 can remove zinc ions from newly imported proteins and from Mia40 thereby improving protein oxidation in the IMS (36,37).

Protein import by the mitochondrial disulfide relay

Mitochondrial preproteins, whether they are directed to the matrix or to the IMS, can be imported into isolated mitochondria in vitro. Hence, an obligatory coupling of protein synthesis and protein translocation (like found for most proteins of the mammalian endoplasmic reticulum) does not apply for mitochondrial protein import. Nevertheless, protein synthesis and protein import still might be kinetically coupled, i.e. proteins might start to be imported while they are still synthesized. This might be achieved by the attraction of nascent chains of polysomes to the surface of mitochondria so that proteins that are produced by downstream ribosomes are synthesized in direct proximity of TOM complexes. In agreement with this concept, it was shown that mRNAs for mitochondrial proteins are enriched in mitochondrial fractions isolated from yeast cells and that – at least for certain transcripts - this enrichment depends on the presence of the preprotein receptor Tom20 (38,39). In addition, yeast mitochondria carry the mRNA-binding protein Puf3 on their surface (40-42). Puf3 binding sites were identified in several 5’-UTR regions of mRNA encoding for mitochondrial proteins, including some IMS proteins like Cox17, Cox23 or Pet191 (Fig. 2). Whether Puf3 binding to mRNA indeed leads to a co-translational protein import or has other functions in the expression of mitochondrial proteins is not known.

Mia40-mediated protein translocation

Substrates need to be in a reduced and unfolded state to be imported into the IMS (43-45). For cytosolic precursors of the small Tim proteins Tim9 and Tim10 it was reported that bound zinc ions stabilize the reduced state of cysteine residues prior to import. However, it is not known whether the zinc ions are removed before import or if proteins enter the IMS in a zinc-containing form (36).

The protein-conducting channel of the TOM complex is believed to serve as general entry site for preproteins into mitochondria. Also IMS proteins apparently employ the TOM pore as blocking the TOM complex with large amounts of matrix-targeted proteins prevented protein import into the IMS (44). Direct binding of substrates of the mitochondrial disulfide relay to TOM receptors was, however, not shown so far. Mia40 plays an essential role for the import of these proteins and serves as a docking factor which binds substrates during or directly after their translocation across the outer membrane (Fig. 2). Preproteins bind to Mia40 by use of specific binding sequences (19). These so-called MISS motifs (consensus aromatic-XX-hydrophobic-hydrophobic-XXC) serve as recognition site that determine which positions of the incoming polypeptides are bound by Mia40 (18,19). Thereby, the MISS motifs presumably positions the sequences in the binding cleft of Mia40 in an orientation that allows the interaction of the redox-active CPC motif of Mia40 with the cysteine residue in the substrate (15,17). In this reaction a mixed disulfide of both proteins is formed as a reaction intermediate (12,13,46). It is conceivable that this strong contact is used to improve preprotein translocation across the outer membrane. In the imported substrate proteins, the sequence around the MISS motif forms a helical region and NMR studies suggest that helix formation is induced or stabilized by Mia40 binding (16). In a final step, formation of an intramolecular disulfide bond leads to the release of the substrates from Mia40 (46). Since only unfolded proteins are able to traverse the TOM pore, oxidative folding traps the proteins stably in the IMS.

Most substrate proteins contain two disulfide bonds. At least in vitro Mia40 can introduce both disulfide bonds in sequential reactions (30). In the presence of oxygen, semioxidized proteins are also further oxidized without additional factors in vitro, but whether this reflects the in vivo situation is unclear (15,16). Mutants in which individual cysteines are mutated can still be oxidized as long as the
MISS signal is not destroyed; in this case, only one disulfide bond is formed (15,30).

In vitro, glutathione plays a critical role in substrate oxidation by Mia40 (30,46). The precise role of glutathione is not clear but the presence of 5 to 10 mM glutathione strongly increases both Mia40-mediated substrate oxidation in the reconstituted system and Mia40-dependent protein import into the IMS. How can a reductant increase the rate of protein oxidation? It was observed that in the absence of glutathione Mia40 accumulated in mixed disulfides which represented kinetically trapped oxidation intermediates. It is conceivable that in these intermediates non-native disulfides are formed and Mia40 can only be released by the help of an isomerase/reductase activity. Glutathione could fulfill this function and thereby serve as a lubricant that ensures that the oxidation pathway will finally lead to a native folded protein. This would also explain why most Mia40 substrates contain two disulfide bonds because these will strongly stabilize the oxidized conformations and make them resistant towards reduction by glutathione. Indeed, IMS proteins like small Tim proteins or twin CX3C proteins (see below) were shown to have very negative redox potentials (-340 to -310 mV) and are only reduced by high concentrations of dithiothreitol or glutathione if boiled in urea or SDS (47). Since so far the strongly stimulating effect of glutathione was only observed in vitro it cannot be excluded that in vivo additional reductants contribute to the folding of IMS proteins (48).

Mia40 oxidation by Erv1

The N-terminal shuttle domain of Erv1 is specifically designed to interact with Mia40 whereas the redox-active cysteine pair in the FAD domain is inaccessible for Mia40 (30,49,50). The sequence around the N-terminal cysteine pair is conserved and forms a helix that resembles the region around the MISS signal in imported proteins. Presumably, imported proteins and Erv1 alternatingly interact with Mia40 thereby cycling it between oxidized and reduced states (Fig. 2) (50). The redox potentials of the substrate proteins (-340 to -310 mV for Tim9, Tim10, Tim13 and Cox17) where found to be very similar to that of the N-terminal domain of Erv1 (-320 mV) (29,33,45,51-53). However, the redox pair in the FAD domain of Erv1 is significantly more positive (-150 mV, hence oxidizing), and presumably drives the oxidation of substrate proteins. It was suggested that Mia40 and Erv1 are associated with each other forming a ternary complex with the substrate in order to mediate substrate oxidation with high efficiency (54).

The substrates of the mitochondrial disulfide relay

The majority of the substrates of the mitochondrial disulfide relay are small proteins with simple helix-loop-helix folds in which the helices are connected by two disulfide bonds (55-58). The cysteines forming these disulfides are spaced by either 3 or 9 amino acid residues. Consequently, the proteins are called twin CX3C and twin CX9C proteins, respectively. In yeast 15 mitochondrial proteins with a twin CX3C motif and five mitochondrial twin CX9C motif proteins were identified most of which are conserved from plants to humans (59-61). The oxidoreductase Mia40 also contains a twin CX3C motif but is of much larger size as other members of the twin CX9C family (59). Notably, bioinformatic analyses suggest the number of twin CX3C proteins in human cells to be at least twice as high (62), while the number of twin CX9C proteins is five in animals and fungi.

Twin CX3C proteins

The members of the twin CX3C family are also referred to as small Tim proteins, a group of import components that are ubiquitously expressed in eukaryotes. Small Tim proteins function as chaperones that facilitate the transport of hydrophobic membrane proteins from the TOM channel through the IMS to their insertion sites at the inner and outer membrane (Fig. 3A) (63-65). The small Tim proteins were shown to form three distinct, heterohexameric complexes of ring-like structure: two soluble complexes formed by Tim9 and Tim10, and by Tim8 and Tim13, respectively, and one Tim9-Tim10-Tim12 complex that is associated with the membrane-embedded TIM22 translocase of the inner membrane (47,58,66,67). Formation of the disulfide bonds within the small Tim proteins was shown to be a prerequisite for their assembly into these complexes (43).

Notably, a mutation of one of the cysteine residues in the human homolog of Tim8, DDP1/TIMM8a has been shown to be the cause for the Mohr-Tranebjaerg (MTS/DFN-1) or deafness/dystonia syndrome,
a progressive neurodegenerative disorder (68,69). In this disease TIMM8a is instable and cannot be detected in patient fibroblasts. Due to a critical function of the Tim8/Tim13 complex in the import of Tim23, the central component of the preprotein translocase of the inner membrane, the absence of TIMM8a results in an impaired protein import into mitochondria and, as a consequence, in a severe pleiotropic mitochondrial dysfunction.

**Twin CX₃C proteins**

While the small Tim proteins play a consistent role in the import of proteins into mitochondria, the functions of twin CX₃C proteins appear to be rather heterogeneous (Fig. 3). Many of the twin CX₃C proteins are linked to the assembly of the cytochrome c oxidase of the respiratory chain (Fig. 3D) (59,60). The copper chaperone Cox17 for example delivers copper to subunits 1 and 2 (Cox1 and Cox2) of cytochrome c oxidase and *in vitro* has been shown to bind Cu(I) in a redox-regulated fashion (70,71). Cox19 and Cox23, which are structurally related to Cox17, are also involved in copper delivery although they may not bind copper directly (72,73). Likewise, the proteins Cmc1 and Cmc2 have recently been shown to be involved in the maturation of cytochrome c oxidase (74,75).

The two twin CX₃C proteins Mdm35 and Som1 are presumably not involved in cytochrome c oxidase assembly. Mdm35 is important for the import of the proteins Ups1, Ups2 and Ups3 into the IMS, three factors that are critical for mitochondrial lipid homeostasis (Fig. 3B) (76,77). In the absence of Mdm35 the three Ups proteins are unstable and substrates for the i-AAA protease Yme1 and Atp23, two IMSlocalized peptidases. The formation of a stable complex between Mdm35 and the Ups proteins ensures their stable accumulation in the IMS.

The protein Som1 is the third subunit of the inner membrane peptidase (Imp) complex (Fig. 3E) (78-81). The Imp peptidase processes as well nuclear encoded substrates (like cytochrome b₂, the cytochrome b₅ reductase Mcr1, the glycerol-3-phosphate dehydrogenase Gut2 and cytochrome c₁) as the mitochondrial encoded protein Cox2. Deletion mutants of *SOM1* show defects in the processing of several Imp substrates (78,82).

**Other IMS proteins with disulfide bonds**

In addition to the twin CX₃C and twin CX₄C proteins the IMS harbors other proteins containing disulfide bonds. These proteins include the superoxide dismutase Sod1 and its copper chaperone Ccs1, the sulfhydryl oxidase Erv1, the complex III subunits Qcr6 and Rieske protein Rip1, the thioredoxin-like proteins Sco1 and Sco2, and the proteins Cox11 and Cox12.

Sod1 and Ccs1 form part of the antioxidative system that dismutates superoxide anions to hydrogen peroxide (Fig. 3F). Sod1 is a dimeric copper- and zinc-containing protein that contains one disulfide bond per subunit. The insertion of this disulfide bond and of the copper ion is facilitated by Ccs1 (83-85). The majorities of both proteins are present in the cytosol, however small amounts are also found in the IMS of mitochondria (84,86,87). It was proposed that Ccs1 mediates the import of Sod1 into the IMS because upregulation of Ccs1 in the IMS results in an increase of Sod1 in this compartment (84). Like Sod1, Ccs1 contains one structural disulfide bond. This disulfide bond is introduced during import by the mitochondrial disulfide relay (88,89,100).

In addition to its two redox-active CXXC motifs, Erv1 contains a structural disulfide bond that is critical for its stability (Fig. 3C). This disulfide bond stabilizes the four helix bundle of Erv1 that is responsible for the binding of the redox cofactor FAD. Notably, Erv1 lacks a mitochondrial presequence and is a substrate of the mitochondrial disulfide relay itself (60,90). However, it remains unclear whether Mia40 introduces the structural disulfide into Erv1.

Complex III of the respiratory chain also harbours two disulfide-containing proteins that face the IMS: Qcr6 (subunit 8 in mammals) and the Rieske iron-sulfur protein Rip1 (Fig. 3D). Qcr6 and subunit 8 are composed of two antiparallel helices that are connected by one or two disulfide bonds, respectively (91), thereby resembling the structure of twin CX₃C proteins. In the catalytic subunit Rip1 the [2Fe-2S] iron-sulfur cluster is held between two loops of the protein that are connected by a disulfide bond (92). This disulfide bond is found in Rieske proteins of all eukaryotes and is critical for enzymatic activity of complex III (93).

In addition, the proteins Cox11 and Cox12 are disulfide-containing proteins of the IMS (Fig. 3D). Cox12 is a part of cytochrome...
c oxidase and its CX_9C-CX_10C cysteine pattern closely resembles the twin CX_9C motifs. Like in these proteins the cysteines form two parallel disulfide bonds. Cox11 is an assembly factor for cytochrome c oxidase that is required for copper insertion (94). It has been proposed that the protein can also exist as a dimer that is stabilized by a disulfide bond (95). The function of Cox11 in copper transfer from Cox17 to Cox1 might be catalytically similar to that of Sco1 and Sco2 in the copper transfer from Cox17 to Cox2 (96). Sco1 and Sco2 are membrane proteins that expose a domain with a thioredoxin-like fold into the IMS (Fig. 3D) (52,97,98). This fold also contains a CX_3C motif that recently has been shown to be redox-active in vivo. It was proposed that Sco2 acts as a thiol-disulfide oxidoreductase that can oxidize the copper-coordinating cysteine residues in Sco1 during Cox2 maturation (99). It remains unclear whether the mitochondrial disulfide relay is involved in the reoxidation of Sco2.

The function of the mitochondrial disulfide relay for the import or folding of these proteins is not well understood. Proteins like Sco1/Sco2, Cox11, Erv1, Rip1 and Sod1/Ccs1 are of very diverse structure suggesting that the protein folding capacity of Mia40 is not limited to simply structured helix-loop-helix proteins. It will be a major task in the future to study the relevance of the mitochondrial disulfide relay for the biogenesis and function of the wide range of IMS proteins.

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FOOTNOTES
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The abbreviations used are: ALR, augmenter of liver regeneration; Ccs1, copper chaperone for Sod1; GFER, growth factor erv1-like; IMS, intermembrane space; ITS, IMS-targeting signal; Mia40, mitochondrial IMS import and assembly pathway 40 kDa; MISS, mitochondria IMS-sorting signal; MTS, matrix targeting signal; Sod1, superoxide dismutase 1; TIM, translocase of the inner membrane; TOM, translocase of the outer membrane.

FIGURE LEGENDS
Figure 1. The components of the mitochondrial disulfide relay. (A) Scheme of Mia40. This oxidoreductase contains a helix-loop-helix domain that is stabilized by two structural disulfide bonds. The domain is preceded by a short helical region that contains the redox active CPC motif. To oxidize its substrates the CPC motif has to be in an oxidized state. Moreover, the substrate should contain a MISS motif that is capable of binding to the hydrophobic groove formed by the helix-loop-helix domain of Mia40. (B) Scheme of Erv1. Erv1 is a homodimeric flavoprotein. Each subunit is composed of two domains: a four-helix bundle FAD domain and a flexible shuttle domain. Both domains contain redox-active CXXC motifs. During the reoxidation of Mia40, the CXXC motif in the shuttle domain of Erv1 forms an intermolecular disulfide with Mia40. Subsequently, electrons are passed onto the CXXC motif in the FAD domain of the other subunit of Erv1. From there electrons are shuttled via the FAD cofactor to cytochrome c. In addition to its redox-active cysteine pairs, Erv1 also contains a structural disulfide bond that stabilizes the four-helix bundle of the FAD domain. The box shows a schematic presentation of the structure of one FAD domain of Erv1.

Figure 2. Import of substrates into the IMS of mitochondria. Substrates of the mitochondrial disulfide relay are synthesized on cytosolic ribosomes and are imported posttranslationally. Notably, there are indications for a localized synthesis of several precursor proteins close to mitochondria ensuring an efficient import into the organelle. The binding of mRNAs to the surface receptor Puf3 might restrict synthesis of some proteins to the mitochondrial surface (Class I), whereas others are synthesized on free ribosomes (Class III) (41). Mia40 substrates can only traverse the TOM complex...
in a reduced and unfolded state, thus the proteins are likely stabilized by chaperones and zinc ions in the cytosol. As soon as the substrates enter the IMS they are recognized by the oxidoreductase and import receptor Mia40 via their MISS motifs. The substrates and Mia40 form mixed disulfide bonds and the substrates are correctly oriented on Mia40. Subsequently, oxidized substrates are released and the now reduced Mia40 is reoxidized by Erv1 allowing the start of a new import cycle.

**Figure 3. Functions of proteins with disulfide bonds in the IMS of mitochondria.** Proteins with disulfide bonds are indicated by bold lettering. Names of substrate proteins that depend on the function or presence of disulfide-containing proteins are indicated in blue. See text for details.
A Mia40

- Redox-active CPC motif
- Hydrophobic binding cleft
- Structural disulfides

B Erv1

- FAD domain
- Shuttle domain
- Intersubunit electron flow between redox-active CXXC motifs
- Redox-active CXXC motif
- FAD cofactor
- Structural disulfides

Fig1-JBC 2011
**Class III:** small Tims
Cox19
Som1
Ccs1
Erv1

**Class I:**
Cox17
Cox23
Pet191
Cmc3

Cytosol

Mia40

Mia40 reoxidation

folded IMS protein

Herrmann Riemer
Fig2-JBC 2011
Translocation of Membrane Protein

Import/Stabilization

Redox-dependent Import

Respiration

Copper Transport and Complex IV Assembly

ROS detoxification

A Translocation of Membrane Protein

B Import/Stabilization

C Redox-dependent Import

D Respiration

E Copper Transport and Complex IV Assembly

F ROS detoxification

Tim9, Tim10, Tim12, Tim8, Tim13

Ups1, Ups2

Mdm35

Mia40

Erv1

MCF/c98-barrel proteins

Cox17, Cox19, Cox23, Cmc1, Cmc2, Coa4, Pet191, Som1

Qcr6, Rlp1, Cox12

Cox12, Cox17, Cox19, Cox23, Cmc1, Cmc2, Coa4, Pet191, Som1

Ccs1

Sod1, H2O2

ROS detoxification

Complex IV Assembly

Copper Transport and Complex IV Assembly

Respiration

Redox-dependent Import

Import/Stabilization

Translocation of Membrane Protein

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