Accessory subunits of mitochondrial complex I

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Abstract
Mitochondrial complex I has a molecular mass of almost 1 MDa and comprises more than 40 polypeptides. Fourteen central subunits harbour the bioenergetic core functions. We are only beginning to understand the significance of the numerous accessory subunits. The present review addresses the role of accessory subunits for assembly, stability and regulation of complex I and for cellular functions not directly associated with redox-linked proton translocation.

Overview
Proton-translocating NADH:ubiquinone oxidoreductase (respiratory complex I) is a very large and complex membrane protein [1]. Fourteen central subunits represent the minimal form of the enzyme and are conserved from bacteria to humans. In complex I from the aerobic yeast Yarrowia lipolytica 28 accessory subunits with a total mass of more than 421 kDa were detected accounting for 44% of the mass of the holoenzyme [2,3]. In bovine complex I, the presence of 30 accessory subunits [4,5] is well established and orthologues have been predicted or detected in human complex I [6,7]. The functional significance of accessory subunits is highlighted by an increasing number of reports on complex I dysfunction connected with this group of subunits [8]. The present review focuses on accessory complex I subunits from human and bovine complex I and from the yeast genetic model Y. lipolytica. These three systems lack a uniform nomenclature and we will indicate all three subunit names throughout (Bt, Hs and Yl subscripts indicate Homo sapiens, Bovine complex I and from the yeast genetic model Y. lipolytica respectively; compare Table 1).

Topology, structure and relationship with other proteins
The architecture of the complete eukaryotic enzyme complex has been characterized by X-ray crystallography [9] and electron microscopy [10,11] (Figure 1). The matrix arm of complex I harbours the NADH oxidation and the ubiquinone reduction module (N-module and Q-module respectively). The membrane arm comprises a proximal and a distal proton pump module (Pp-module and Pd-module, respectively). Structural information on individual accessory subunits is still very limited. High-resolution structures were determined by NMR spectroscopy for NDUFA2Hs, N18M17/B8Bt [12] and alphaproteobacterial homologues [13] of subunit NUMM1Hs/NDUF6Hs:13-kDaBt expressed in Escherichia coli (Northeast Structural Genomics Project), and, using a cell-free expression system (Riken Structural Genomics Project), for the acyl carrier domain of the human ACPM (mitochondrial acyl carrier protein) that was detected as subunit NDUFAB1Hs in human complex I [6]. Subunit NUENMI/NDUFA9Hs:39-kDaBt belongs to the structurally well-characterized short-chain dehydrogenase family and comprises an NADPH-binding site [14]. Subunits NB4MI/B14Bt/NDUFA6Hs and N12M15/B12Bt/NDUF9Hs are members of the Lyr (leucine/tyrosine/arginine) protein family extensively discussed in the review by Angerer [14a] in this issue of Biochemical Society Transactions.

A topological model for the arrangement of subunits in complex I has been derived from proteomic analysis of different subcomplexes and sequence-based targeting predictions [3]. Accessory complex I subunits can be divided into three different groups: (i) hydrophilic subunits of the matrix arm, (ii) membrane arm subunits with single or multiple transmembrane domains, STMD [15] and MTMD respectively, and (iii) subunits associated with the membrane arm but without transmembrane domains (Table 1). In the latter group, subunits can be exposed to either the matrix or the intermembrane space side. Subunits NB8M15/NDUFB7Hs/B18Bt, NIPIM17/NDUFS5Hs/PFFDFBt and NUPM15/NDUFA8Hs/PGVIBt contain a conserved pattern of cysteine residues (double CX2C) in the case of NUPM15/NDUFA8Hs/PGVIBt, quadruple CX2C that is a hallmark of polypeptides imported to the intermembrane space by the Mia40 import system (reviewed in [16]); structural models for all three subunits have been calculated [17] and the electron-density maps of Y. lipolytica complex I show an extensive layer of mostly helical protein mass on the intermembrane space side of the membrane arm [9]. Mammalian complex I subunits PDSWBt/NDUFB10Hs...
Table 1 | Accessory subunits of mitochondrial complex I

<table>
<thead>
<tr>
<th>Subunit Name</th>
<th>Y. lipolytica (kDa)</th>
<th>Human†</th>
<th>Bovine‡ (kDa)</th>
<th>Remarks</th>
<th>Associated disease(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Matrix arm (N-module and Q-module)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NUEM (40.4)</td>
<td>NDUFA9</td>
<td>39-kDa (39.1)</td>
<td>NADPH-binding short-chain dehydrogenase; active–deactive transition</td>
<td>Leigh syndrome [75]</td>
<td></td>
</tr>
<tr>
<td>NUM (19.8)</td>
<td>NDUFA7</td>
<td>B14.5a (12.6)</td>
<td>Related to assembly factor N7BML (NDUFAF2)</td>
<td>Leigh syndrome [76]</td>
<td></td>
</tr>
<tr>
<td>N7BM (16.2)</td>
<td>NDUFA12</td>
<td>B17.2 (17.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NUJM (15.9)</td>
<td>NDUFS4</td>
<td>AQQDQ§ (15.3)</td>
<td>Phosphorylation</td>
<td>Leigh-like syndrome [8,73,74]</td>
<td></td>
</tr>
<tr>
<td>NUFM (15.6)</td>
<td>NDUFA5</td>
<td>B13 (13.2)</td>
<td>Active–deactive transition</td>
<td>Autism [77,78]</td>
<td></td>
</tr>
<tr>
<td>NB4M (14.6)</td>
<td>NDUFA6</td>
<td>B14 (15.0)</td>
<td>Lyr protein LYRM6 nitration, see Angerer [14a]</td>
<td>Down-regulated in HIV infection [79]</td>
<td></td>
</tr>
<tr>
<td>NUMM (13.1)</td>
<td>NDUFS6</td>
<td>13-kDa (10.5)</td>
<td>Putative Zn²⁺ -binding site PDB codes of bacterial homologues: 2JVM, 2JRR, 2JZ8</td>
<td>Fatal neonatal acidaemia [23,80]</td>
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</tr>
<tr>
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<td>–</td>
<td>–</td>
<td>Acyl carrier protein, compare PDB code 2DNW</td>
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<td></td>
</tr>
<tr>
<td>NI8M (9.5)</td>
<td>NDUFA2</td>
<td>B8 (11.0)</td>
<td>PDB code 1S3A</td>
<td>Leigh syndrome [81]</td>
<td></td>
</tr>
<tr>
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<td>NDUVF3</td>
<td>10-kDa (8.4)</td>
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<td></td>
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<td><strong>P₃-module</strong></td>
<td></td>
<td></td>
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<tr>
<td>NUPM (19.2)</td>
<td>NDUFA8</td>
<td>PGIV (20.0)</td>
<td>Quadruple CysC</td>
<td>Target of viral RNA [50] and proteins [48,49], tumorigenesis [42,82,83]</td>
<td></td>
</tr>
<tr>
<td>NUXM (18.6)</td>
<td>–</td>
<td>–</td>
<td>MTMD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NB6M (14.0)</td>
<td>NDUFA13</td>
<td>B16.6 (16.6)</td>
<td>STMD, phosphorylation, in humans and cows identical with GRIM-19, regulation of cell death</td>
<td>Infante lactic acidaemia, encephalocardiomyopathy [90]</td>
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</tr>
<tr>
<td>NIMM (9.7)</td>
<td>NDUFA1</td>
<td>MWFE (8.1)</td>
<td>STMD, phosphorylation, assembly</td>
<td>Leigh-like syndrome, neurodegeneration [84–86]</td>
<td></td>
</tr>
<tr>
<td>NI9M (9.0)</td>
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<td>B9 (9.3)</td>
<td>STMD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEBM (7.9)</td>
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<td></td>
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<tr>
<td><strong>P₅-module</strong></td>
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</tr>
<tr>
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<td>NDUFB11</td>
<td>ESSS (14.5)</td>
<td>STMD, phosphorylation, neuronal differentiation, see [87]</td>
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<td></td>
</tr>
<tr>
<td>NUJM (20.7)</td>
<td>NDUFA11</td>
<td>B14.7 (14.8)‡</td>
<td>MTMD, related to TIM 17,22, 23, see [88]; dual location in plant, see [89]</td>
<td></td>
<td></td>
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<td>NIAM (14.6)</td>
<td>NDUFB8</td>
<td>ASHI (18.7)</td>
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<td></td>
<td></td>
</tr>
<tr>
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<td>–</td>
<td>–</td>
<td>STMD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIZM (12.9)</td>
<td>NDUFB9</td>
<td>B22 (21.7)</td>
<td>Lyr protein LYRM3; see Angerer [14a]</td>
<td>Muscular hypotonia and raised blood lactate level [91]</td>
<td></td>
</tr>
<tr>
<td>NB8M (11.1)</td>
<td>NDUFB7</td>
<td>B18 (16.5)</td>
<td>Double CysC, myristoylated, see [92]</td>
<td></td>
<td></td>
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<td>NIDM (10.9)</td>
<td>NDUFB10</td>
<td>PDSW (20.8)</td>
<td>Phosphorylation</td>
<td></td>
<td></td>
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<tr>
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<td>NDUFB4</td>
<td>B15 (15.1)</td>
<td>STMD, nitration</td>
<td></td>
<td></td>
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<td>ACPM2 (10.1)</td>
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<tr>
<td>NNP (9.9)</td>
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<td>PFFD, 15-kDa (12.5)</td>
<td>Double CysC</td>
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<tr>
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<td>–</td>
<td>STMD</td>
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<tr>
<td>NB2M (6.8)</td>
<td>NDUFB13</td>
<td>B12 (11.0)**</td>
<td>STMD, methylated, see [92]</td>
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<tr>
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<td>SGDH (16.7)</td>
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<tr>
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<td>NDUFB6</td>
<td>B17 (15.5)</td>
<td>STMD†</td>
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<tr>
<td>–</td>
<td>NDUFC2</td>
<td>B14.5b (14.1)††</td>
<td>MTMD†, phosphorylation</td>
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<td></td>
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Table 1 | Continued

<table>
<thead>
<tr>
<th>Y. lipolytica* (kDa)</th>
<th>Human†</th>
<th>Bovine‡ (kDa)</th>
<th>Remarks</th>
<th>Associated disease(s)</th>
</tr>
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<tr>
<td>–</td>
<td>NDUFB2</td>
<td>AGGG (8.5)</td>
<td>STMD††</td>
<td></td>
</tr>
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<td>NDUFB1</td>
<td>MNLL (7.0)</td>
<td>MTMD††</td>
<td></td>
</tr>
<tr>
<td>Localization unclear</td>
<td></td>
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<tr>
<td>ST1 (34.6)</td>
<td>–</td>
<td>–</td>
<td>Sulfur transferase</td>
<td></td>
</tr>
<tr>
<td></td>
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<td>42 kDa (36.7)</td>
<td></td>
<td>Iα subcomplex phosphorylation</td>
</tr>
<tr>
<td></td>
<td>NDUFAB1</td>
<td>SDAP (10.7)</td>
<td></td>
<td>Acyl carrier protein, compare PDB code</td>
</tr>
<tr>
<td></td>
<td>NDUFC1</td>
<td>KFYI (5.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Position and molecular masses of mature proteins according to [3].
†Molecular masses of mature proteins according to [18].
‡Subunit composition according to [6] and as reviewed in [7].
§Designation 18 kDa subunit is used frequently instead.
∥Initial designation NUWM.
¶Not determined; calculated mass in parentheses.
**Two masses reported.
††Topology prediction for human complex I using HMMTOP [94].

Figure 1 | Architecture of mitochondrial complex I

The matrix arm comprises the N-module (yellow) and the Q-module (orange). Iron-sulfur clusters (blue spheres) transfer electrons from the initial acceptor FMN to the ubiquinone reduction site (Q/QH2, ubiquinone in oxidized and reduced form). The membrane arm is divided into a PP-module and a PD-module respectively.

and B22Bt/NDUFB9Hs each comprise two pairs of cysteine residues. However, unorthodox CX_C intervals question processing by the Mia40 import machinery.

Recent evidence suggests that the matrix arm of Y. lipolytica complex I comprises nine hydrophilic accessory subunits, presumably including NB4M13 (B14Bt/NDUFA6Hs) and the acyl carrier protein subunit ACPM1Yl ([3], and H. Angerer, M. Radermacher, M. Mańkowska, M. Steger, K. Zwicker, H. Heide, U. Brandt and V. Zickermann, unpublished work) (Table 1). Despite overall consistency in subunit composition the following differences to the matrix arm of complex I from the mammalian enzyme should be noted. The mammalian 10-kDa subunit (NDUFV3Hs) is known to be associated with the flavoprotein fragment harbouring the NADH oxidation site [18] is not present in Y. lipolytica complex I. The position of the acyl carrier protein subunit SDAPBt/NDUFA1Hs in mammalian complex I is ambiguous because it was found in different subcomplexes of the enzyme. The Y. lipolytica NUEM subunit was detected in a matrix arm fragment, but the orthologous bovine 39-kDa subunit is absent from the corresponding bovine subcomplex Iα. As this may rather reflect a different fragmentation behaviour, there is no compelling evidence to assume a difference in subunit position between complex I from the two organisms. The PP-module of Y. lipolytica complex I contains four STMD subunits and one MTMD subunit. Only three of these five membrane-intrinsic subunits are found in the mammalian enzymes; the position of subunit NUPMYl (NDUFA8Hs/PGIVBt) at the ‘heel’ of complex I was demonstrated by electron microscopy [3]. The PD-module contains six STMD subunits, one MTMD subunit and five hydrophilic polypeptides in Y. lipolytica complex I. Several more membrane-intrinsic subunits have been assigned to the corresponding Iβ subcomplex of bovine complex I [18] (Table 1). The position of subunit NESM13 (ESSS13/NDUFB11Hs) was determined by electron microscopy [19]. The P0-module of Y. lipolytica contains a second ACPM, ACPM2. This position is in agreement with the presence of bovine subunit SDAP in subcomplex Iβ [18], but at variance with its concomitant detection in subcomplex Iα that includes the matrix arm. Moreover, it is impossible to conclude unambiguously from sequence alignments whether the bovine subunit is more similar to Y. lipolytica ACPM1 or ACPM2 (results not shown).

Function

Complex I assembly and stability
Absence of a functional NDUF5Hs subunit (AQDQHs/NUYM13) has been shown to interfere with complex I assembly resulting in formation of a ~830-kDa subcomplex.
of an 18-kDa protein assigned to subunit NDUF4Hs (NUYMYl/AQDQBt) by PKA was first described and linked with stimulation of complex I activity by Papa and colleagues (reviewed in [35]). However, the identity of the labelled protein was challenged by Chen et al. [36] who identified subunit ESSSb (NDUF4H11/NESM11) to represent the 18-kDa species. In the same experiment, cAMP/PKA-dependent phosphorylation of subunit MWFEb (NIMMYl/NDUFA1Hb) was demonstrated. Phosphorylation of subunit ESSS after cAMP/PKA treatment of bovine heart mitochondria was confirmed [32]; however, the physiological significance remains unclear because the phosphorylated serine residue is not conserved throughout even in mammalian complex I [36]. The impact of phosphorylation of subunits ESS and MWFE on complex I assembly was investigated by site-directed mutagenesis [37]. Evidence for phosphorylation of subunit NDUF4Hb (NUYMYl/AQDQB) in isolated complex I is still lacking, but it has been pointed out that the subunit of mammalian complex I does contain a conserved canonical PKA phosphorylation site (C-terminal RVSTK) [38] and its functional significance was tested experimentally [38]. The mechanism of complex I regulation by phosphorylation of NDUF4Hb (NUYMYl/AQDQB) has been suggested to involve stimulation of mitochondrial precursor protein import and maturation of the subunit permitting assembly into nascent complex I or exchange of subunit(s) of damaged enzyme [39,40].

**GRIM-19, STAT3 and the IFN/RA pathway**

Investigating the growth-suppressive action of the combination of IFNβ (interferon β) and RA (all-trans-retinoic acid) Angell et al. [41] identified GRIM-19 as a cell death regulatory gene product. Overexpression of GRIM-19 enhanced IFN/RA-induced cell death. In contrast, antisense knockdown protected against cell death in response to IFN/RA [41]. The functional characteristic of GRIM-19 as a tumour-suppressor gene and its role in tumorigenesis has been reviewed recently [42]. The bovine homologue of GRIM-19 was identified as accessory subunit B16.6b of mitochondrial complex I [43] and the presence of GRIM-19/NDUFA13Hb as a bona fide subunit of human complex I was confirmed later [6]. In line with this finding, but in contrast with a previously determined nuclear localization [41], GRIM-19 has been found to reside primarily in mitochondria [44]. Tight association of subunit NDUFA13Hb (B6M11/B16.6b; GRIM-19) with the matrix arm in subcomplex Iα and the presence of one predicted transmembrane segment suggests a position in the Pδ-module of the membrane arm of complex I [3,43]. Gene deletion resulted in severe disruption of complex I assembly causing early embryonic lethality [44]. Functional domains of the subunit were dissected by truncation, deletions and point mutations [41,45]. The homologous B6M subunit of *Y. lipolytica* complex I lacks part of the functionally important C-terminal domain [1]. It has been suggested that GRIM-19 is a ‘dual-function’ protein and might play a role as a complex I subunit and as a cell death regulatory
protein, but the link between these two functions, if any, remains to be established. Two studies independently demonstrated the interaction of GRIM-19 with STAT3 (signal transducer and activator of transcription 3), a latent cytoplasmic transcription factor that is activated by cytokines and growth factors, but different modes of interaction have been suggested [46,47]. Interestingly, GRIM-19 is the target of several viral factors that interfere with its central function in regulation of cell death [48,49]. A 2.7 kb non-coding RNA from HCMV (human cytomegalovirus) has been reported to interact with complex I via GRIM-19 protecting infected cells against apoptosis, apparently by preventing relocalization of the complex I subunit to the nucleus [50]. In contrast, a mechanism for IFN/RA-linked induction of apoptosis with a central function of ROS (reactive oxygen species) overproduction and excluding shuttling of GRIM-19 to the nucleus has been suggested in [51]. Recently, the unprecedented presence of STAT3 in mitochondria and STAT3-dependent modulation of mitochondrial energy metabolism has been demonstrated [52–54]. However, very low relative abundance renders significant regulatory effects by direct interaction of STAT3 with complex I unlikely [55]. In conclusion, a clear and consistent picture reconciling all observations on the function of GRIM-19 is still lacking.

A (active)-D (deactive) transition
Mitochondrial complex I from various species has been shown to undergo a reversible A–D transition and the A and D forms of complex I can be distinguished by differential accessibility of a specific cysteine residue in the long loop connecting transmembrane helices 1 and 2 of subunit ND3 [56]. It has been suggested that the fungal 29.9 kDa subunit corresponding to subunit NUFM57/NDUFA5h/B13b is involved in modulation of the A–D transition [57]. Recently, differential cross-linking in the A and D states has been observed for the ND3 and the 39-kDa (NDUFA9Hs/NUEM51) subunits [58], suggesting a position at the interface between the membrane arm and the peripheral arm.

Acyl carrier proteins and biosynthetic pathways
The small and highly acidic SDAPb subunit (NDUFAB1b) of bovine complex I was identified as an acyl carrier protein, and the presence of a covalently attached phosphopanthetine prosthetic group was demonstrated [59]. In contrast with human and bovine complex I, Y. lipolytica complex I comprises two acyl carrier protein subunits: ACPM1 and ACPM2 [60]. Deletion of ACPM1Yl appears to be lethal for Y. lipolytica, whereas deletion of ACPM2Yl strongly interferes with complex I assembly [60]. The latter observation is in agreement with results obtained for Neurospora crassa [61]. Given their high sequence similarity, the lack of cross-complementation between ACPM1 and ACPM2 in Y. lipolytica complex I seems remarkable.

Mitochondria harbour all of the necessary functional elements for fatty acid synthesis resembling the type II mode of their bacterial ancestors (reviewed in [62]). In this context, two functions involving mitochondrial acyl carrier proteins are discussed. Several lines of evidence suggest mitochondrial synthesis of octanoic acid as a precursor of lipoic acid, a prosthetic group of, e.g., the mitochondrial pyruvate dehydrogenase and 2-oxoglutarate (α-ketoglutarate) dehydrogenase complexes. Lipoic acid administration fails to compensate for functional disruption of endogenous cofactor synthesis [63]. The second or alternative function is synthesis of longer-chain fatty acids [64] that might be critical for repair of damaged membrane lipids [65,66] or modification of proteins, e.g., myristoylation. It should be noted that the function of the SDAP subunit is very likely not to be dependent on a physical link with complex I as the major fraction of the polypeptide was detected in free form in the mitochondrial matrix [66]. Moreover, none of the three ACPMs detected in Arabidopsis thaliana is associated with complex I [67], and the presence of an ACPM was established in Saccharomyces cerevisiae, a species lacking respiratory complex I [68].

Pathogenic mutations and complex I dysfunction
Oxidative stress is associated with neurodegenerative human diseases and has been suggested to be a key determinant in biological aging [69,70]. Several complex I subunits are targeted by reactive nitrogen species including accessory subunits B15b (NDUF8Hb/NB5hMyl), B14b (NDUF6Hb/NB4hMyl) and B17.2b (NDUFA12Hb/ N7hMyl) [71]. Induction of necrotic cell death was found to be linked with nitration of accessory subunit NDUF8Hb (ASH1b/NIAM51) [72].

All accessory subunits and the seven central subunits located in the peripheral arm as well as all complex I assembly factors are nuclear-encoded. Pathogenic mutations in nuclear genes have been reviewed recently [8], and diseases linked with dysfunction of accessory complex I subunits are summarized in Table 1. Nuclear mutations causing severe complex I defects were reported for eight accessory subunits. In most cases, they cause Leigh or Leigh-like syndrome, a multisystemic and progressive neurodegenerative disorder. Subunit NDUF4Hb stands out as a hotspot with 14 patients and ten affected families described in the literature [73,74]. These numbers are comparable with the highest frequency of observations for central subunits NDUF5Hb (75-kDaM51 subunit, ten cases), NDUF5Hb (49-kDaM51 subunit, 15 cases) and NDUFV1Hb (51-kDaM51 subunit, 17 cases) [8].

Summary and outlook
A substantial fraction of the total mass of mitochondrial complex I is represented by accessory subunits, and evidence is accumulating that they are integral and indispensable components of the enzyme complex. The focus of future research will be to gain insights into the functional and structural interaction of accessory and central subunits at the
molecular level to comprehensively understand the striking complexity of mitochondrial complex I.

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