Minireview

The respiratory complex I of bacteria, archaea and eukarya and its module common with membrane-bound multisubunit hydrogenases[1]

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Received 19 June 2000; accepted 27 June 2000

Edited by Vladimir Skulachev

Abstract The proton-pumping NADH:ubiquinone oxidoreductase, also called complex I, is the first of the respiratory complexes providing the proton motive force which is essential for energy consuming processes like the synthesis of ATP. Homologues of this complex exist in bacteria, archaea, in mitochondria of eukaryotes and in chloroplasts of plants. The bacterial and mitochondrial complexes function as NADH dehydrogenase, while the archaeal complex works as $F_{420}H_2$ dehydrogenase. The electron donor of the cyanobacterial and plastidal complex is not yet known. Despite the different electron input sites, 11 polypeptides constitute the structural framework for proton translocation and quinone binding in the complex of all three domains of life. Six of them are also present in a family of membrane-bound multisubunit [NiFe] hydrogenases. It is discussed that they build a module for electron transfer coupled to proton translocation.

Key words: NADH:ubiquinone oxidoreductase; Complex I; [NiFe] hydrogenase; Modular evolution; Iron–sulfur cluster; Respiratory chain; Energy conservation

1. Introduction

The proton-pumping NADH:ubiquinone oxidoreductase, also called respiratory complex I, is the first of the respiratory chain complexes providing the proton motive force required for energy consuming processes like the synthesis of ATP. This multisubunit complex catalyzes the electron transfer from NADH to ubiquinone linked with proton translocation across the membrane:

$$NADH + Q + 5\ H_n^+ \rightarrow NAD^+ + QH_2 + 4\ H_p^+ \quad (1)$$

where Q refers to ubiquinone, and H_n^+ and H_p^+ to the protons taken up from the negative inner and delivered to the positive outer side of the membrane [1–4]. The complex from *Klebsiella pneumoniae* and *Escherichia coli* may also pump Na^+ ions [5,6]. Complex I is characterized by its prosthetic groups, namely one FMN and up to nine iron–sulfur (FeS) clusters, its large number of subunits, and its sensitivity to a variety of natural compounds like rotenone or piericidin A [1,7,8]. Homologues of complex I exist in bacteria, archaea and eukarya [3]. For simplicity, we will use the term complex I for the homologous enzymes in all three domains of life throughout this review.

Sequence analysis revealed the modular structure of complex I. It became clear that complex I evolved from preexisting modules for proton translocation and electron transfer [3,9]. One of these modules is shared with the today's [NiFe] hydrogenases. Hydrogenases catalyze the interconversion of molecular hydrogen and two protons plus two electrons:

$$2\ H^+ + 2\ e^- \rightarrow H_2 \quad (2)$$

All known [NiFe] hydrogenases contain a large subunit with the [NiFe] active site and a small subunit coordinating one or more tetranuclear FeS cluster(s) [10,11]. Hydrogen is activated at the [NiFe] active site and the FeS cluster(s) mediate electron transfer between the active site and the redox partners like cytochromes and ferredoxins. The large and the small subunit show a weak but distinct sequence similarity to subunits of the respiratory complex I. This homology was first discovered by Böck and coworkers [12,13] and was confirmed later by others [14,15].

From the increasing number of known protein sequences, a group of membrane-bound multisubunit [NiFe] hydrogenases was identified [16]. These hydrogenases are build up by at least six subunits (Table 1) which are all homologous to complex I subunits. The small and large subunits of these hydrogenases show a higher degree of sequence identity to the corresponding complex I subunits than to the soluble [NiFe] hydrogenases [9]. From these data, we concluded that complex I and the membrane-bound multisubunit [NiFe] hydrogenases share a common ancestor [9].

This minireview focuses on the composition of the complex I homologues in bacteria, archaea and eukarya and the module common to complex I from all three domains of life as well as to the membrane-bound [NiFe] hydrogenases. For a more comprehensive discussion of complex I and hydrogenases, see [10,11,17].

2. Complex I of bacteria, archaea and eukarya

Within the domain of bacteria, complex I is found in all

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[1] Dedicated to Prof. Dr. Hanns Weiss on the occasion of his 60th birthday.

Abbreviations: F_{420}, (*N*-L-lactyl-γ-L-glutamyl)-L-glutamic acid phosphodiester of 7,8-didemethyl-8-hydroxy-5-deazariboflavin-5′-phosphate; $F_{420}H_2$, reduced F_{420}

0014-5793/00/$20.00
PII: S0014-5793(00)01867-6

subdivisions of proteobacteria [3]. Generally, 14 genes specify the minimal structural framework of a proton-pumping NADH:ubiquinone oxidoreductase in this class. They are organized in one operon or cluster. The complex I genes and the derived proteins are called *nuoA–N* (from NADH:ubiquinone oxidoreductase; or *nqo1–14* from NADH:quinone oxidoreductase). The order of the 14 *nuo* genes is conserved among the proteobacteria. As an exception to this rule, several clusters of *nuo* genes exist in *Rickettsia prowazekii*, which is more closely related to mitochondria than any other studied microbe [18]. *Sinorhizobium meliloti* contains a second set of *nuo* genes, which are present in three gene clusters (P. Putnoky, personal communication). The *nuo* genes encode seven peripheral proteins including the subunits that bear all known redox groups of complex I. The remaining seven subunits are most hydrophobic proteins predicted to fold into 54 α-helices across the membrane. Little is known about their function, but they are most likely involved in proton translocation [9].

The *nuo* gene clusters of *Helicobacter pylori* (accession numbers: NC000915 and NC000921) as well as of *Campylobacter jejuni* (accession number: NC002163) from the ε-subdivision of proteobacteria are missing the homologues of *nuoE* and *F*, and contain a modified *nuoG* [19]. Remarkably, these three genes encode subunits comprising the NADH dehydrogenase part, a conserved structural and functional unit of complex I containing the FMN and four EPR-detectable FeS clusters [3,20]. This unit is believed to represent a conserved NADH dehydrogenase/diaphorase module. Therefore, the proton-pumping quinone oxidoreductase from *H. pylori* and *C. jejuni* most likely accepts electrons from another donor than NADH.

The spreading of complex I within the domain of bacteria is not limited to proteobacteria. Homologues of all 14 *nuo* genes are also present in the Gram-positive bacteria *Streptomyces coelicolor* (accession number: AL078618) and *Mycobacterium tuberculosis* (accession number: AL123456), in *Thermus thermophilus* [21] and *Deinococcus radiodurans* R1 (accession number: AE00513) from the *Thermus/Deinococcus* group, and in the hyperthermophilic bacterium *Aquifex aeolicus* (accession number: NC000918) from the genus *Aquifex*. The genes *nuoE* and *F*, and *nuoG* are located at separate loci in *A. aeolicus*, one of the earliest diverging bacteria known. This might indicate that the NADH dehydrogenase part was adapted to an ancestral donor:quinone oxidoreductase during evolution (see below).

Most eukaryotes with the exception of a few fermentative yeasts contain a proton-pumping NADH:ubiquinone oxidoreductase in their mitochondrial respiratory chain which was adapted from a bacterial progenitor by endosymbiosis [3]. The subunit composition of the mitochondrial complex I is extraordinary complex. It contains up to 28 extra subunits in addition to the homologues of the 14 complex I subunits of proteobacteria [1,2]. The homologues of the seven hydrophobic subunits (NuoA, H and J–N, Table 1) are mitochondrially encoded in all eukaryotes. The seven predominantly peripheral proteins (NuoB–G and I, Table 1) are nuclear-encoded in most animals, plants and fungi. In some eukaryotes, the homologues of NuoB, C, D, G and I are mitochondrially encoded [9,22].

The many extra proteins seem to be a special feature of the mitochondrial complex I. They are all nuclear-encoded and show a weak but distinct sequence similarity between bovine and *Neurospora crassa*. It has been speculated that these subunits form a scaffold around the 14 minimal subunits preventing the high energy electrons from escaping the complex and forming reactive oxygen species [23]. Two of the extra proteins may have a special biosynthetic function [20,24].

Cyanobacteria contain homologues of 11 bacterial *nuo* genes (Table 1), while three genes encoding the NADH dehydrogenase part of complex I are missing [3,9]. Therefore, the complex I homologue involved in photosynthetic electron transfer seems to be equipped with a different electron input device. Either ferredoxin, NADH or NADPH might be the electron donor implying that the cyanobacterial complex might alternatively work as a ferredoxin:plastoquinone oxidoreductase or NAD(P)H:plastoquinone oxidoreductase [3,25].

Chloroplasts contain a homologue of complex I which resembles the one of cyanobacteria. Homologues of the 11 cy-

Table 1
Nomenclature and localization of homologous subunits of the bacterial (*E. coli*) and mitochondrial (*Bos taurus*) NADH:ubiquinone oxidoreductase [3], the cyanobacterial complex from *Synechocystis* PCC6803 [3], the archaeal $F_{420}H_2$:methanophenazine oxidoreductase from *M. mazei* [31] and the Ech hydrogenase from *M. barkeri* [36]

Designation of the subunit					Localization	Predicted function
E. coli	*B. taurus*	*Synechocystis*	*M. mazei*	*M. barkeri*		
NuoA	ND3	NdhC	FpoA	–	membraneous	
NuoB	PSST	NdhK	FpoB	EchC	peripheral	[4Fe4S]
NuoC[a]	30 (IP)	NdhJ	FpoC	EchD	peripheral	
NuoD[a]	49 (IP)	NdhH	FpoD	EchE	peripheral	H^+ channel; [NiFe] cluster[b]
NuoE	24 (IP)	–	–	–	peripheral	[2Fe2S]
NuoF	51 (FP)	–	–	–	peripheral	NADH binding; FMN; 2×[4Fe4S]
NuoG	75 (IP)	–	–	–	peripheral	[4Fe4S]; 1 (2)[c]×[2Fe2S]
NuoH	ND1	NdhA	FpoH	EchB	membraneous	quinone binding
NuoI	TYKY	NdhI	FpoI	EchF	peripheral	2×[4Fe4S]
NuoJ	ND6	NdhG	FpoJ	–	membraneous	
NuoK	ND4L	NdhE	FpoK	–	membraneous	
NuoL	ND5	NdhF	FpoL	EchA	membraneous	H^+ translocation
NuoM	ND4	NdhD	FpoM	–	membraneous	H^+ translocation
NuoN	ND2	NdhB	FpoN	–	membraneous	H^+ translocation
–	–	–	FpoO	–	peripheral	[2Fe2S]
–	–	–	FpoF	–	peripheral	FAD; 2×[4Fe4S]

[a]The genes of NuoC and NuoD are fused to one gene *nuoCD* in *E. coli* [9].
[b]The [NiFe] cluster is present only in the [NiFe] hydrogenases.
[c]NuoG of *E. coli* contains an additional [2Fe2S] cluster [3].

anobacterial *nuo* gene homologues are also present in the plastidal genome of higher plants and liver worth [3,9]. All efforts failed to demonstrate the existence of the three genes encoding the NADH dehydrogenase part. A complex I preparation from pea thylakoids contains 16 subunits, five of them are supposed to be nuclear-encoded [26]. The preparation contains polypeptides with molecular masses similar to the ones that build the NADH dehydrogenase module, however, their identity remains obscure. If the plastidal complex should contain the NADH dehydrogenase module, it must have been acquired by a separate evolutionary event, since this module is not present in cyanobacteria [27]. Analysis of tobacco disruption mutants suggests that the plastidial complex like the cyanobacterial one is involved in a cyclic electron flow around photosystem I in the light and most likely in chlororespiration in the dark [25,28,29].

Homologues of the 11 *nuo* genes present in cyanobacteria have also been found in archaea (Table 1) while the genes encoding the NADH dehydrogenase module are missing as well [30–32]. The function of this module has most likely been taken over by a $F_{420}H_2$ ((*N*-L-lactyl-γ-L-glutamyl)-L-glutamic acid phosphodiester of 7,8-didemethyl-8-hydroxy-5-deazariboflavin-5′-phosphate) dehydrogenase. This protein oxidizes $F_{420}H_2$, the major cytoplasmic electron carrier of methanogens and a reversible hydride donor like NADH [31]. The $F_{420}H_2$ dehydrogenase like the NADH dehydrogenase module converts a two electron transfer from a hydride donor to two one electron transfers to FeS clusters. Therefore, the archaeal complex I homologue most likely functions as a $F_{420}H_2$:quinone oxidoreductase.

Homologues of the 11 *nuo* genes and one gene encoding the $F_{420}H_2$ dehydrogenase subunit form one cluster in the hyperthermophilic sulfate-reducing archaeon *Archeoglobus fulgidus* [30]. It has been shown that the $F_{420}H_2$:menaquinone oxidoreductase complex is the main generator of proton motive force in *A. fulgidus* [33]. A $F_{420}H_2$:methanophenazine oxidoreductase has been described in the methanogenic archaeon *Methanosarcina mazei* [31]. This complex contains two genes encoding a $F_{420}H_2$ dehydrogenase part in addition to the 11 *nuo* homologues (Table 1). The electron acceptor of this complex has recently been identified as methanophenazine, a hydrophobic redox-active 2-hydroxyphenazine with an ether-bridged polyisoprenoid side chain [31]. The electron input part of the complex I homologue in the crenarchaeon *Aeropyrum pernix* is not known, since no gene encoding a dehydrogenase is located in close vicinity to the 11 *nuo* gene homologues [32].

3. The module common to complex I and the membrane-bound multisubunit [NiFe] hydrogenases

From the above mentioned, it can be concluded that the 11 genes which are present in the complex I homologues of all three domains of life build the structural framework for proton translocation and quinone binding (Table 1), while various modules for a reversible electron transfer constitute the electron input part of the complex. Homologues of six of these 11 genes are also present in the family of multisubunit membrane-bound [NiFe] hydrogenases (Table 1). This family includes the hydrogenase 3 and 4 of the formate hydrogenlyase system of *E. coli* [12,34], the CO-induced hydrogenase of *Rhodospirillum rubrum* [35] and the Ech hydrogenase of *Methanosarcina barkeri* [36]. These hydrogenases seem to participate in similar physiological reactions, namely the transfer of reducing equivalents generated by the oxidation of a low-potential electron donor to protons which are subsequently reduced to hydrogen [13,35,37]. This reaction is most likely coupled with the generation of a proton motive force [16, 35,36]. *Methanobacterium thermoautotrophicum* and *Methanococcus jannaschii* contain two members of this hydrogenase family each, with a putative function in endergonic reactions like the synthesis of acetyl-CoA [16]. Homologous sequences are also found twice in the genome of *Pyrococcus horikoshii* (accession number: NC000961), in *Pyrodictium abyssi* (accession number: AL096836), and in the thermophilic eubacterium *Thermotoga maritima* (accession number: AE000512) with yet unknown physiological functions.

The homology concerns the predominantly peripheral subunits NuoB, C, D and I and the membraneous subunits H and L (Table 1). NuoC is very weakly conserved and is not present in the four hydrogenases from *M. thermoautotrophicum* and *M. jannaschii*. These hydrogenases contain neither a homologue of NuoI but genes that encode several polyferredoxins which might fulfil a similar function [16]. The complex I subunits NuoL, M and N stem from a common ancestor [20], making it difficult to discern their corresponding homologues in the hydrogenases. The hydrogenases from *M. thermoautotrophicum* and *M. jannaschii* contain 10 and nine additional hydrophobic subunits, respectively [16]. The hydrogenase 4 of *E. coli* comprises three additional hydrophobic subunits [34]. None of these subunits contains a known sequence motive for cofactor binding. In some cases, *nuoC* is fused to *nuoD* in complex I as well as in the membrane-bound hydrogenases [9].

The six subunits common to complex I and the membrane-bound [NiFe] hydrogenases may build a module for the transfer of one electron coupled with the translocation of one proton. Within this module, electrons are transferred from the two tetranuclear FeS clusters on NuoI to the FeS cluster on

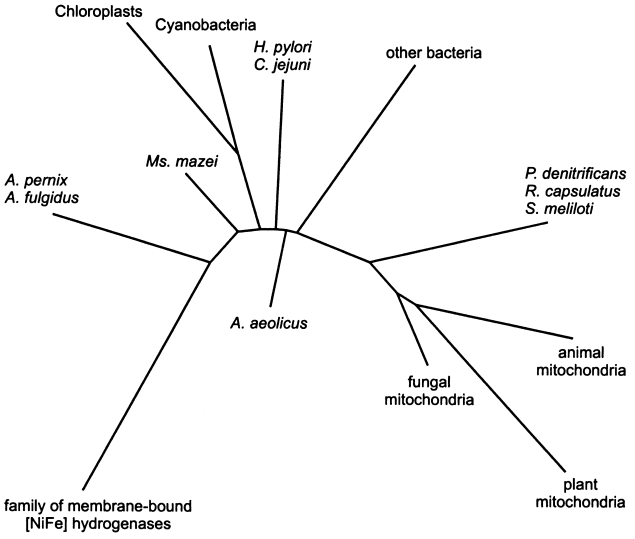

Fig. 1. Consensus tree derived from unrooted evolutionary trees of the NuoB, C, D, H and I homologues. The sequences were aligned with ClustalX and the phenograms were calculated with Phylip [43,44]. The individual evolutionary trees are shown on our web-site (http://www.uni-duesseldorf.de/WWW/MathNat/biochem).

NuoB. In the hydrogenase, they are passed on to the [NiFe] active site located on the NuoD homologue of the hydrogenases. This cofactor is missing in complex I [38]. The further electron route in complex I may lead to the quinone binding site. It is discussed that NuoD together with NuoH and NuoB are involved in quinone binding in complex I [39,40]. Proton translocation across the membrane might be accomplished by NuoL being related to Na^+ or K^+/H^+ antiporters [9]. As the membrane-bound hydrogenases do not react with quinones [37], proton translocation accomplished by this module seems to be independent on ubiquinone. The H^+/e^- stoichiometry of complex I has been determined to be two [41,42], indicating that complex I most likely comprises another energy coupling site in addition to the site provided by the module described above.

4. Modular evolution of complex I

To obtain information about the possible evolution of complex I and the [NiFe] hydrogenases, we estimated phylogenies from the protein sequences of the Nuo homologues using the programs ClustalX (Vers. 1.62b, 43) and Phylip (Vers. 3.5c, 44). A crude consensus tree derived from the trees of the sequences of the individual subunits is shown in Fig. 1. As expected, the mitochondrial complexes cluster together with the bacterial ones. They branch off from the *Paracoccus denitrificans*, *Rhodobacter capsulatus* and *S. meliloti* lineage. A few subunits of the *E. coli* complex are located separately from the homologous subunits of other bacteria. *H. pylori* and *C. jejuni*, which adapted a different NADH dehydrogenase module (see above), branch off separately. *A. aeolicus* containing the genes of the NADH dehydrogenase part on separate loci (see above) builds an own branch. The cyanobacterial and plastidal complexes show roughly the same distance to the bacterial and the archaeal homologues. Unexpectedly, the $F_{420}H_2$:menaquinone oxidoreductase from *M. mazei* does not cluster together with the two other archaeal homologues. The sequences of a few *M. mazei* subunits build the deepest branch among the cyanobacterial and plastidal lineage. The sequences from the euryarchaeon *A. fulgidus* and the crenarchaeon *A. pernix* are most similar to the sequences of the membrane-bound multisubunit [NiFe] hydrogenases, which cluster as one block (Fig. 1).

As it is expected for such a huge and complex enzyme, complex I is assembled from different preexisting modules [3,9]. Complex I evolved from electron transfer proteins (the progenitors of NuoB and D), which are also present in nowadays soluble hydrogenases (Fig. 2). The combination with the progenitors of the ferredoxin NuoI, the quinone binding protein NuoH and the ion-translocating protein NuoL gave rise to a common ancestor of complex I and the membrane-bound multisubunit hydrogenases. This ancestral enzyme might have worked already as a proton-pumping hydrogen:ferredoxin oxidoreductase.

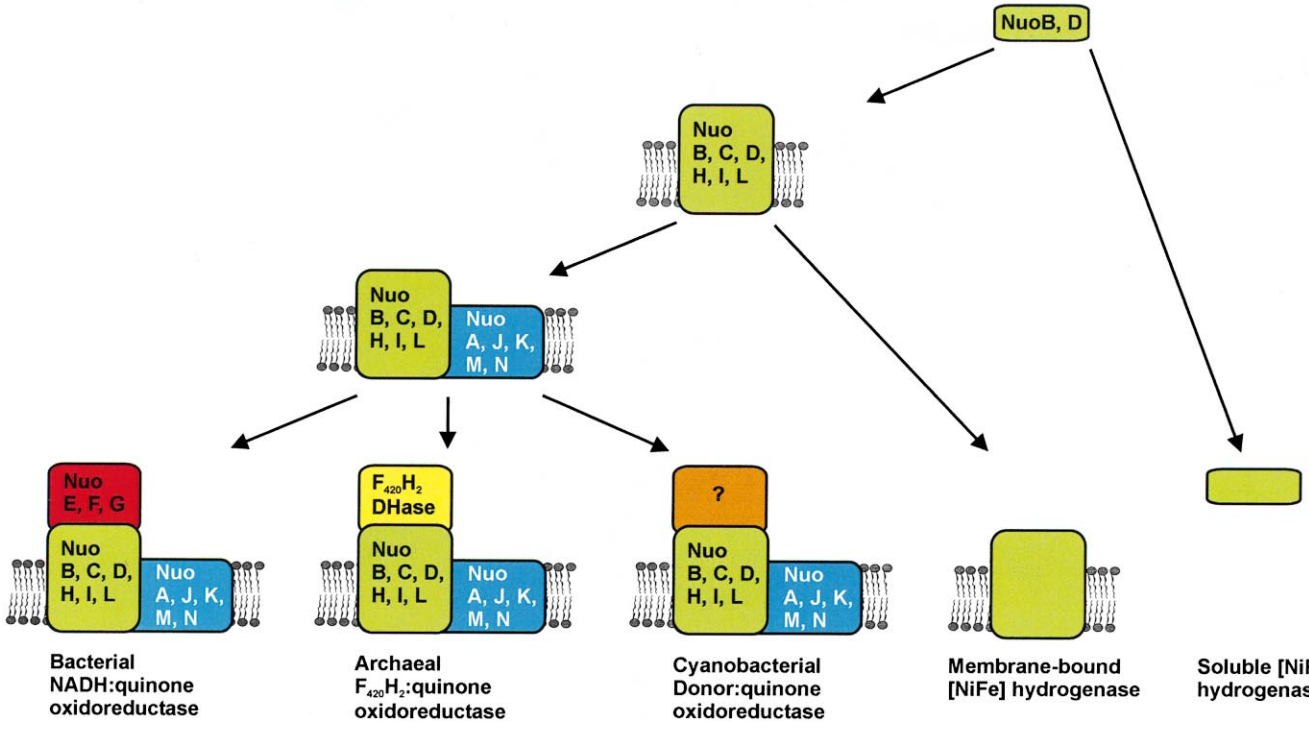

Fig. 2. Hypothetical scheme of modular evolution of complex I. An ancestral hydrogenase made up by the progenitors of NuoB and D evolved by addition of a ferredoxin (NuoI), a transport protein (the progenitor of NuoL, M and N), a quinone binding protein (NuoH) and protein of a yet unknown function (NuoC). This led to the formation of the progenitor of complex I and the membrane-bound hydrogenases. By addition of other membraneous proteins and the individual substrate binding proteins, the membrane-bound multisubunit [NiFe] hydrogenases may have evolved. On the route to complex I, this ancestor lost the [NiFe] active site but was equipped with further proteins by triplication of the transporter related to NuoL and addition of NuoA, J and K. It gained the ability to react with quinone. This progenitor of bacterial, archaeal and eukaryotic complex I may have worked as a ferredoxin:quinone oxidoreductase. The bacterial and the archaeal complex I emerged by acquisition of the NADH dehydrogenase module (NuoE–F) and the $F_{420}H_2$ dehydrogenase module (FpoO and F), respectively. The nature of the module adapted to build the cyanobacterial complex is not yet known. The hydrogenase module is shown in green, the transporter module in blue, and the different electron input modules in orange, yellow and gold, respectively.

Upon evolutionary division, the membrane-bound hydrogenases were equipped with individual substrate binding proteins and a few with other membraneous subunits (Fig. 2). The progenitor of complex I lost its [NiFe] active site and its ability to react with hydrogen. It most likely gained a quinone binding site. The membrane part of the complex was equipped with further membrane proteins by triplication of the transporter subunit NuoL and acquisition of the subunits NuoA, J and K. Thus, the common ancestor of donor:quinone oxidoreductases of bacteria, archaea and eukarya emerged. This complex of 11 subunits might have worked as a ferredoxin:quinone oxidoreductase, but due to its more sophisticated membrane part, may have achieved an additional energy coupling site.

Adaptation of the NADH dehydrogenase module (NuoE, F and G) led to the formation of the proton-pumping NADH:ubiquinone oxidoreductase present in bacteria and mitochondria. The NADH dehydrogenase module is also present in various bacterial and archaeal $NAD(P)^+$-depending hydrogenases and formate dehydrogenases [3,9]. Because these are soluble, non-energy converting enzymes, it is unlikely that this module contributes to energy coupling in complex I.

The adaptation of the $F_{420}H_2$ dehydrogenase subunit to the ancestral donor:quinone oxidoreductase led to the formation of the archaeal $F_{420}H_2$:menaquinone or $F_{420}H_2$:methanophenazine oxidoreductase (Fig. 2). The complex from *M. mazei* has a H^+/e^- stoichiometry of 1 due to the thermodynamic limits given by the midpoint potentials of $F_{420}H_2$ (−360 mV) and methanophenazine (−255 mV) [31]. It is not known whether the second coupling site present in the NADH:ubiquinone oxidoreductase has been lost in the $F_{420}H_2$:quinone oxidoreductase during evolution.

It remains an open question whether the complex I homologue of cyanobacteria was equipped with the NADH dehydrogenase module or the ferredoxin:NADPH reductase as a new electron input module or whether it evolved by alterations of the already existing hydrogenase module.

Acknowledgements: We would like to thank Dr. P. Putnoky, Biological Research Center, Szeged, and Dr. U. Deppenmeier, University of Göttingen for sharing unpublished data. This work was supported by the Deutsche Forschungsgemeinschaft.

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