Subsystem: Succinate dehydrogenase

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- The super-macromolecular respiratory complex II (succinate:quinone oxidoreductase) couples the oxidation of succinate in the matrix / cytoplasm to the reduction of quinone in the membrane. This function directly connects the Krebs cycle and the aerobic respiratory chain. In general, it consists of three to four different subunits and contains one FAD, three distinct types of FeS cluster, and one or two protoheme IX molecules as prosthetic groups.
- Subunits containing bound FAD and iron-sulfur centers constitute a peripheral portion of complex II, which can function as a water-soluble succinate dehydrogenase upon release from membranes. The reverse reaction (reduction of fumarate) functions as an electron sink in anaerobic respiration.
- Two smaller membrane-spanning subunits (or one as in the *Bacillus subtilis* enzyme) are required for the succinate:quinone oxidoreductase activity. One of them, cytochrome B, has one or two ptotohaem group(s). Membrane-anchor subunits are variable and are represented by several non-ortologous proteins. This has functional implications. For instance, cytochrome b_{558} has the highest redox potential and can support both succinate dehydrogenase and fumarate reductase activities. Cytochrome b_{560} correlates with the lowest fumarate reductase activity of the complex.
- Fumarate:quinol oxidoreductase complex may contain two (as in *E.coli*) or one (as in *Helicobacter pylori*) specific hydrophobic anchor proteins. The presence of genes encoding these proteins within a fumarate reductase gene cluster generally indicates that the corresponding protein complex is a virtually unidirectional fumarate reductase.

Subsystem: Succinate dehydrogenase (SDH)

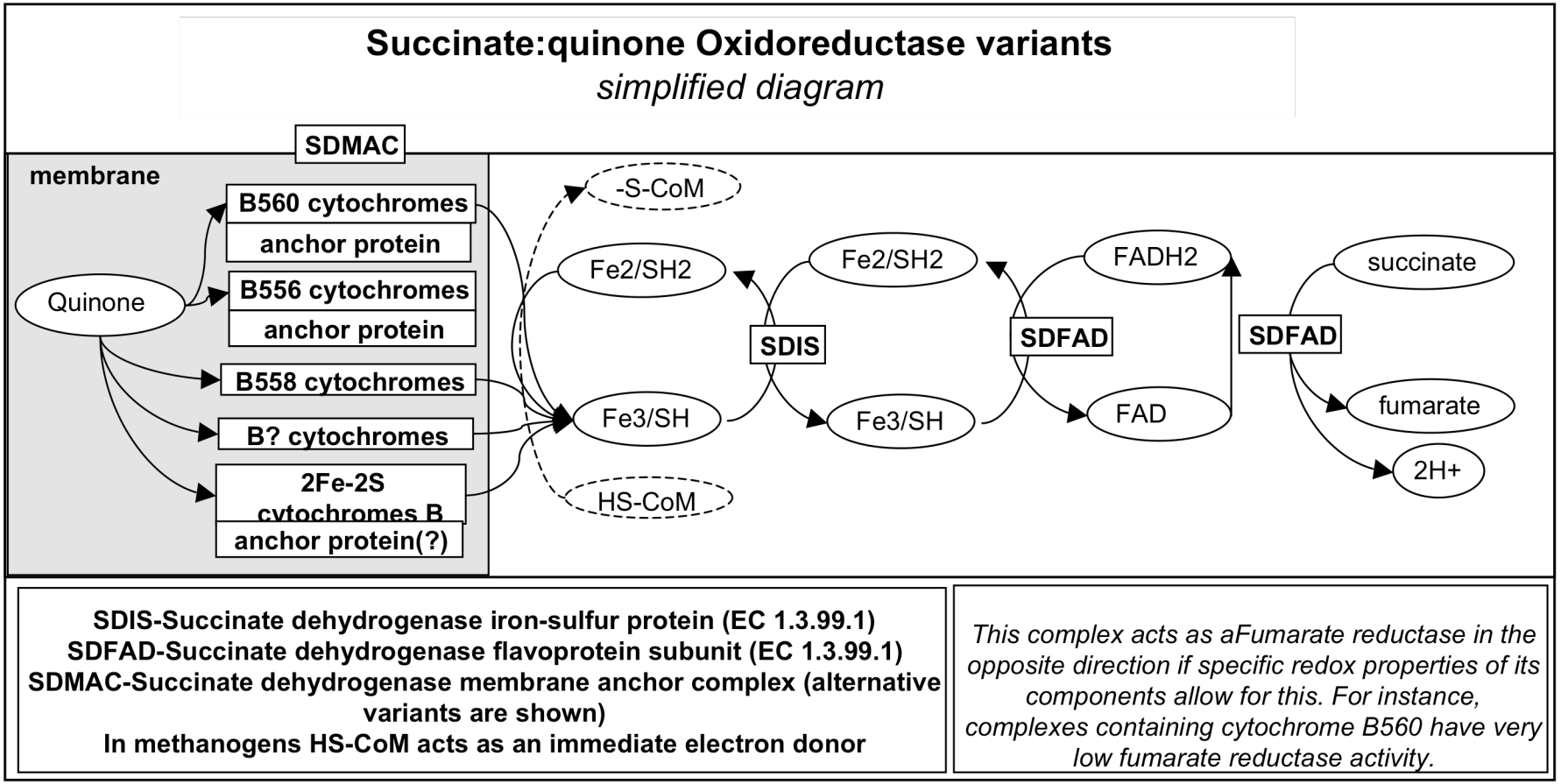
Column	Abbrev	Functional Role
1	SD556	Succinate dehydrogenase cytochrome b-556 subunit
2	SDIS	Succinate dehydrogenase iron-sulfur protein (EC 1.3.99.1)
3	SDFAD	Succinate dehydrogenase flavoprotein subunit (EC 1.3.99.1)
4	SDM	Succinate dehydrogenase hydrophobic membrane anchor protein
5	SDC2	Succinate dehydrogenase cytochrome b subunit
6	pSdhC	Putative succinate dehydrogenase cytochrome b subunit
7	HSDM	Hypothetical succinate dehydrogenase membrane anhor protein
8	FRC	Fumarate reductase subunit C
9	FRD	Fumarate reductase subunit D
10	SDMN	Succinate dehydrogenase hydrophobic membrane anchor protein(Nostoc p.)
11	SD558	Succinate dehydrogenase cytochrome b558 subunit
12	FRCB	Fumarate reductase cytochrome b subunit
13	SD560	Succinate dehydrogenase cytochrome b560 subunit
14	SD560p	Succinate dehydrogenase cytochrome b560 subunit, mitochondrial precursor

SDH membrane anchor proteins →

SDH cytochrome B subunits →

Subset	Includes These Roles
*SDAP	4,7,10
*SDC	1,5,6,11,13,14
Fumarate_reductase	2,3,8,9,12
SDH	1,2,3,4,5,6,7,10,11,13,14

Subsystem diagram



Examples of subsystem functional variants in different genomes

Variant codes:

1-4 subunit succinate dehydrogenase (2 catalitic+2 anchor subunits)

2-4 subunit fumarate reductase

3-4 subunit succinate dehydrogenase and 4 subunit fumarate reductase

4-3 subunit succinate dehydrogenase and 3 subunit fumarate reductase

5-3 subunit succinate dehydrogenase (or, in some cases, fumarate reductase?)

6-4 subunit succinate dehydrogenase and 3 subunit fumarate reductase

7-3 subunit fumarate reductase

Basic Spreadsheet

Organism	Variant Code	*SDC	SDIS	SDFAD	*SDAP	FRC	FRD	FRCB
Escherichia coli 042 [B]	3	470-1	2587 473	2588 472	471-4	2586	2585	
Synechocystis sp. PCC 6803 [B]	5	2451-6	1192 2564	940	?			
Anabaena variabilis ATCC 29413 [B]	5	5984-6	4686	4956	?			
Prochlorococcus marinus MED4 [B]	0							
Bacillus subtilis subsp. subtilis str. 168 [B]	5	2848-11	2846	2847				
Nostoc punctiforme [B]	1	5352-6	1073	2879	702-10			
Haemophilus somnus 2336 [B]	2		789	788		790	791	
Halobacterium sp. NRC-1 [A]	1	1193-5	1191	1190	1192-4			
Helicobacter hepaticus ATCC 51449 [B]	7		687	686				685
Caenorhabditis elegans [E]	0	9078-14	5595	19542 2263	5980-4			
Campylobacter jejuni subsp. jejuni NCTC 11168 [B]	4	407-6	378 406	377 405				376

Quinone:Succinate Oxidoreductase

Fumarate reductase: presence of specific anchor subunits in gene cluster distinguishes it

Subsystem Spreadsheet (fragment)

Specific functional roles were assigned to different membrane anchor subunits of the complex:

Cytochrome B-556

Heterodisulfide Reductase homolog

Cytochrome B-558

Cytochrome B-?

Cytochrome B-560

Basic Spreadsheet

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Prochlorococcus marinus MED4 [B]	0							
Bacillus subtilis subsp. subtilis str. 168 [B]	5	2843-11	2846					
Nostoc punctiforme [B]	1	6352-6	1073	2879	702-10			
Haemophilus somnus 2336 [B]	2		789	788		790	791	
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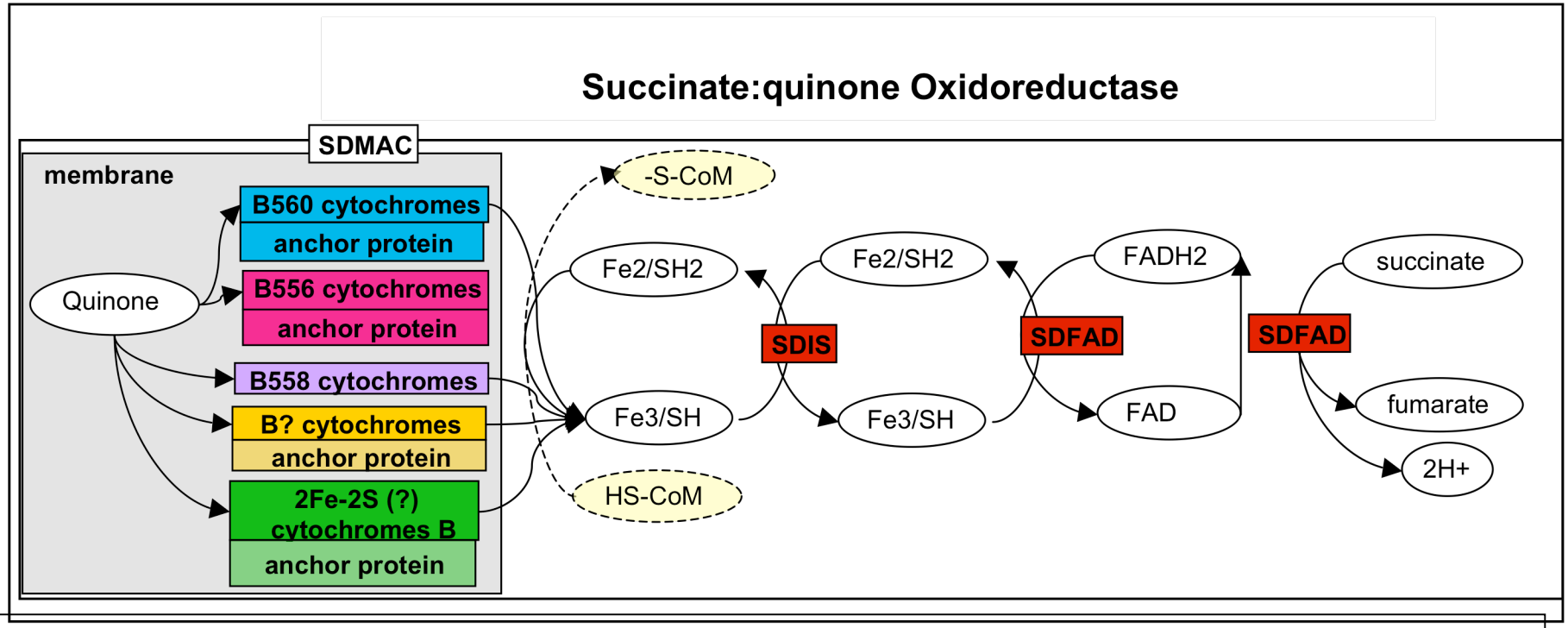
New putative variant of an anchor protein from *Nostoc*

the *E. coli* variant of anchor protein

Occurrence of various membrane anchor subunits in different organisms



Color coding:

- *Eucarya, Rickettsia, Xylella, Xanthomonas, etc*
- *Escherichia, Pseudomonas, Mycobacteria, etc*
- *Sulfolobus, Synechocystis, Nostoc, Chlorobium*
- *Corynebacteria,Halobacterium, Prochlococcci,Thermoplasma, etc*
- *Bacilli, Staphylococci, Chlamidia, etc*
- *Methanobacteria*
- *Archaea*
- **Conserved subunits**

Open questions, comments, conjectures

1. Missing genes

- Succinate dehydrogenase anchor protein is missing in some organisms. Several gene candidates for this role identified in this study (as hypothetical membrane proteins clustered with known succinate dehydrogenase genes) have been included in the subsystem as "Hypothetical succinate dehydrogenase membrane anchor proteins". However, anchor protein is still missing in cyanobacteria (should it be there at all?)
- There are no NCBI records available pertaining to cyanobacterial Succinate dehydrogenase cytochrome b subunit. We were able to predicted an alternative form based on long-range homology in *Prochlorococci, Synechococcus, Chlorobium* and some other bacteria.
- *Synechocystis, Nostoc, Crocosphaera, Trichodesmium* and *Thermosynechococcus* posess the second putative candidate for the role of Succinate dehydrogenase cytochrome b subunit, homologous to a *Sulfolobus* protein formerly annotated as Heterodisulfide reductase -- s*ee next slide*.

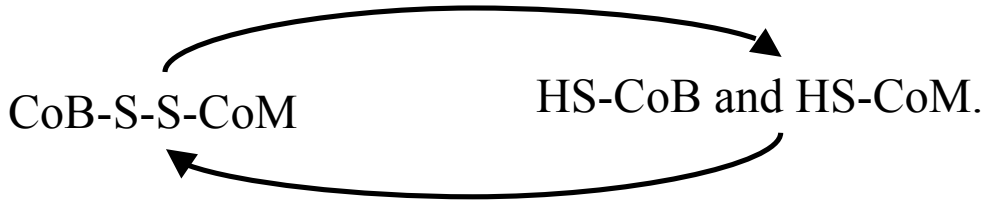
Open questions, comments, conjectures

2. Succinate dehydrogenase and Heterodisulfide reductase evolutionary interplay

Sulfolobus solfataricus P2 [A]	0	2144-6	2143	2142	2145-4
Sulfolobus tokodaii str. 7 [A]	0	552-6	551	550	553-4
Synechocystis sp. PCC 6803 [B]	5	2451-6	1192 2564	940	
Anabaena variabilis ATCC 29413 [B]	5	5984-6	4686	4956	

30%Homology to Heterodisulfide reductase (*Methanobacteria*)

In *Methanobacteria* HS-CoB and HS-CoM are direct soluble electron donors for fumarate reductase



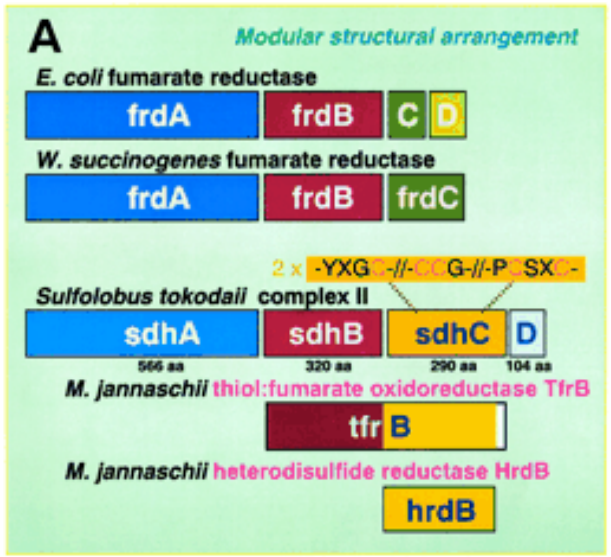
Fumarate → Succinate

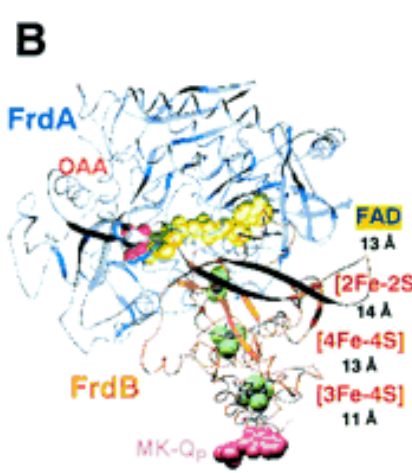
Methanothermobacter thermautotrophicus str. Delta H [A]	0	1811	1471

Succinate dehydrogenase and Heterodisulfide reductase evolutionary interplay continued

At some point during evolution the Heterodisulfide reductase has probably formed a complex with functionally relevant catalytic subunits of fumarate reductase. Disappearance of the heterodisulfide reduction pathway (as a result of the switch from methanogenesis?) lead to further evolution of this protein into a specialized succinate dehydrogenase subunit, as the one now present in Sulfolobus and cyanobacteria.

Fig1 from ***From Iwasaki et al, J. Biol. Chem., Vol. 277, 42, 39642-39648***





A, modular subunit arrangements of selected bacterial Frd complexes, S. tokodaii SdhABCD complex, and subunits of related enzymes (thiol:fumarate oxidoreductase and heterodisulfide reductase) from methanogenic archaea. B, the common cofactor arrangement (FAD and three FeS clusters) in bacterial FrdAB subcomplexes based on the reported crystal structures (5, 6). The FrdA/SdhA subunit contains the dicarboxylate active site at a covalently linked FAD, and the FrdB/SdhB subunit contains a high potential [2Fe-2S] cluster (Center S-1), a low potential [4Fe-4S] cluster (Center S-2), and a high potential [3Fe-4S] cluster (Center S-3) (1, 2, 4). The [3Fe-4S] cluster is replaced by a lower potential [4Fe-4S] cluster in the S. tokodaii SdhB subunit (13).