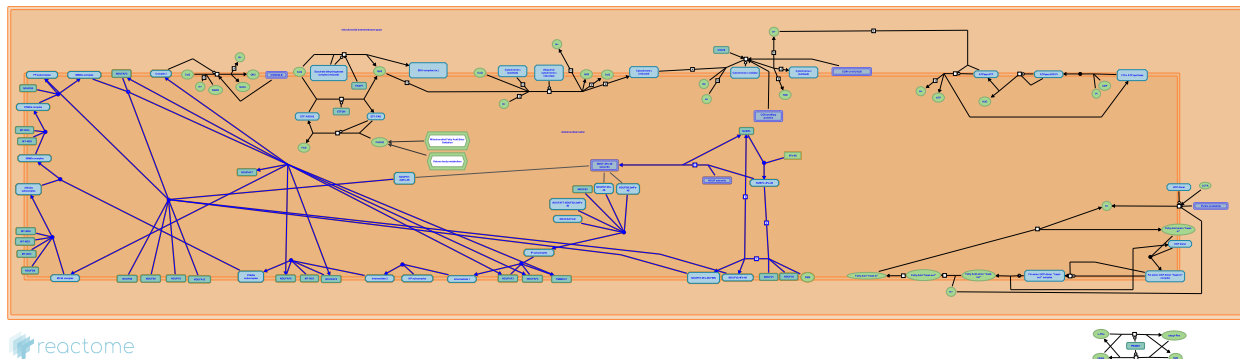


Complex I biogenesis



Jassal, B., Meldal, BH.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

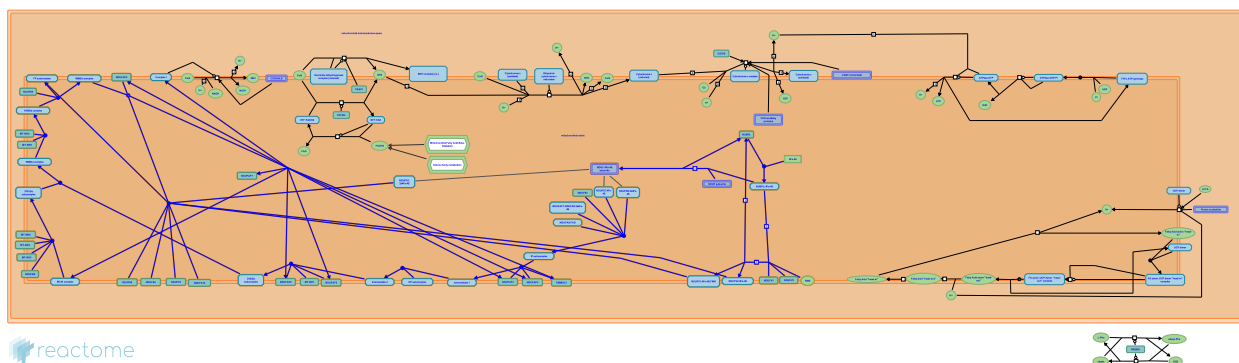
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- Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology*, 14, e1005968. [↗](#)

Reactome database release: 74

This document contains 1 pathway and 13 reactions ([see Table of Contents](#))

Complex I biogenesis ↗

Stable identifier: R-HSA-6799198



Complex I (NADH:ubiquinone oxidoreductase or NADH dehydrogenase) utilises NADH formed from glycolysis and the TCA cycle to pump protons out of the mitochondrial matrix. It is the largest enzyme complex in the electron transport chain, containing 45 subunits. Seven subunits (ND1-6, ND4L) are encoded by mitochondrial DNA, the remainder encoded in the nucleus. The enzyme has a FMN prosthetic group and 8 Iron-Sulfur (Fe-S) clusters. The subunits are assembled together in a coordinated manner via pre-assembled subcomplexes to form the mature holoenzyme. The so-called "assembly factor" proteins, acting intrinsically or transiently, are required for constructing complex I although their exact roles in the biogenesis are not fully understood (Fernandez-Vizarra et al. 2009, McKenzie & Ryan 2010, Mimaki et al. 2012, Andrews et al. 2013).

Literature references

- Andrews, B., Carroll, J., Ding, S., Fearnley, IM., Walker, JE. (2013). Assembly factors for the membrane arm of human complex I. *Proc. Natl. Acad. Sci. U.S.A.*, 110, 18934-9. ↗
- Fontanesi, F., Soto, IC., Horn, D., Barrientos, A. (2006). Assembly of mitochondrial cytochrome c-oxidase, a complicated and highly regulated cellular process. *Am. J. Physiol., Cell Physiol.*, 291, C1129-47. ↗
- McKenzie, M., Ryan, MT. (2010). Assembly factors of human mitochondrial complex I and their defects in disease. *IUBMB Life*, 62, 497-502. ↗
- Mimaki, M., Wang, X., McKenzie, M., Thorburn, DR., Ryan, MT. (2012). Understanding mitochondrial complex I assembly in health and disease. *Biochim. Biophys. Acta*, 1817, 851-62. ↗

Editions

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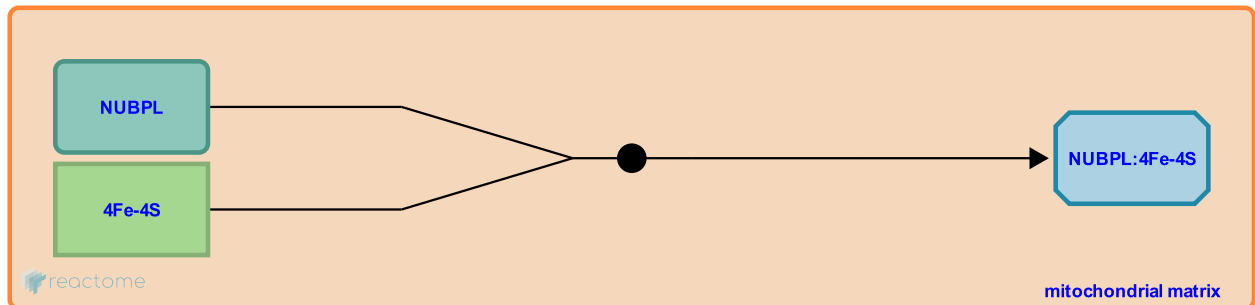
NUBPL binds 4Fe-4S ↗

Location: [Complex I biogenesis](#)

Stable identifier: R-HSA-5690023

Type: binding

Compartments: mitochondrial matrix



The iron-sulfur protein NUBPL is thought to bind the cofactor [4Fe-4S] cluster and deliver it to complex I (NADH dehydrogenase) subunits during its biogenesis. The exact mechanism of transfer is unknown but defects in NUBPL are shown to cause mitochondrial complex I deficiency (MT-C1D) with a distinct MRI pattern (Sheftel et al. 2009, Kevelam et al. 2013).

Followed by: [NUBPL transfers 4Fe-4S to NDUFV1, V2](#), [NUBPL transfers 4Fe-4S to Complex I subunits](#)

Literature references

Sheftel, AD., Stehling, O., Pierik, AJ., Netz, DJ., Kerscher, S., Elsässer, HP. et al. (2009). Human ind1, an iron-sulfur cluster assembly factor for respiratory complex I. *Mol. Cell. Biol.*, 29, 6059-73. ↗

Kevelam, SH., Rodenburg, RJ., Wolf, NI., Ferreira, P., Luning, RJ., Nijtmans, LG. et al. (2013). NUBPL mutations in patients with complex I deficiency and a distinct MRI pattern. *Neurology*, 80, 1577-83. ↗

Editions

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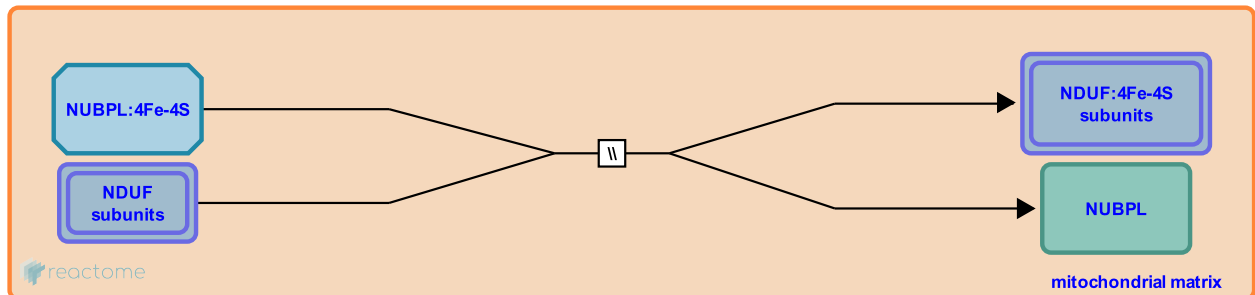
NUBPL transfers 4Fe-4S to Complex I subunits ↗

Location: [Complex I biogenesis](#)

Stable identifier: R-HSA-6788523

Type: omitted

Compartments: mitochondrial matrix



In total, eight iron-sulfur (4Fe-4S) clusters are incorporated into six subunits (mitochondrial matrix-located NDUFs1, S2, S7, S8 and mitochondrial membrane-located V1 and V2) (Andrews et al. 2013). Incorporation into NDUFV1 and V2 (located on the mitochondrial membrane) is shown in a separate reaction. The mechanism of transfer in all cases is unknown.

Preceded by: [NUBPL binds 4Fe-4S](#)

Followed by: [NDUF subunits bind to form the IP subcomplex](#), [NDUF subunits bind to form the FP subcomplex](#)

Literature references

Andrews, B., Carroll, J., Ding, S., Fearnley, IM., Walker, JE. (2013). Assembly factors for the membrane arm of human complex I. *Proc. Natl. Acad. Sci. U.S.A.*, 110, 18934-9. ↗

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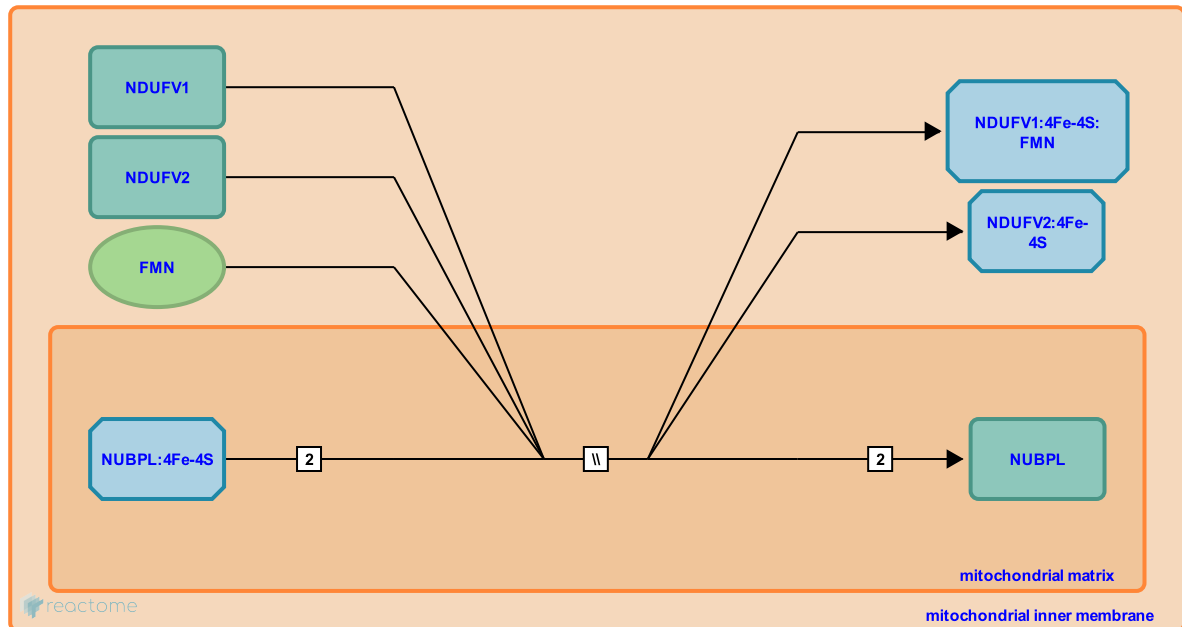
NUBPL transfers 4Fe-4S to NDUFV1, V2 ↗

Location: [Complex I biogenesis](#)

Stable identifier: R-HSA-6788556

Type: omitted

Compartments: mitochondrial matrix, mitochondrial inner membrane



In total, eight iron-sulfur (4Fe-4S) clusters are incorporated into six subunits (mitochondrial matrix-located NDUFV1, S2, S7, S8 and mitochondrial membrane-located V1 and V2) (Andrews et al. 2013). Incorporation into NDUFV1, S2, S7 and S8 is shown in a separate reaction. The mechanism of transfer is unknown. NDUFV1 also binds FMN (Schuelke et al. 1998).

Preceded by: [NUBPL binds 4Fe-4S](#)

Followed by: [NDUF subunits bind to form the FP subcomplex](#)

Literature references

Andrews, B., Carroll, J., Ding, S., Fearnley, IM., Walker, JE. (2013). Assembly factors for the membrane arm of human complex I. *Proc. Natl. Acad. Sci. U.S.A.*, 110, 18934-9. ↗

Schuelke, M., Loeffen, J., Mariman, E., Smeitink, J., van den Heuvel, L. (1998). Cloning of the human mitochondrial 51 kDa subunit (NDUFV1) reveals a 100% antisense homology of its 3'UTR with the 5'UTR of the gamma-interferon inducible protein (IP-30) precursor: is this a link between mitochondrial myopathy and inflammation?. *Biochem. Biophys. Res. Commun.*, 245, 599-606. ↗

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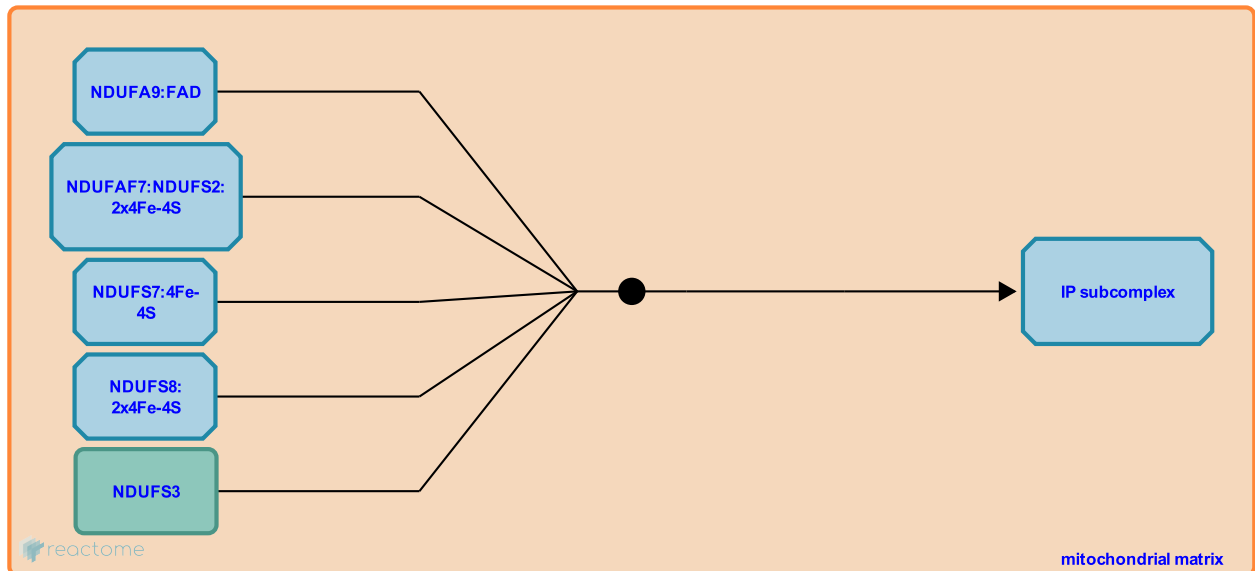
NDUF subunits bind to form the IP subcomplex ↗

Location: [Complex I biogenesis](#)

Stable identifier: R-HSA-6800868

Type: binding

Compartments: mitochondrial matrix



The subunits NDUFS7, S8 and A9, together with NDUFS2 and S3, form an evolutionarily conserved hydrogenase module as part of the Iron-Sulfur protein fraction (IP) subcomplex (Mckenzie & Ryan 2010, Andrews et al. 2013).

Preceded by: [NUBPL transfers 4Fe-4S to Complex I subunits](#)

Followed by: [IP subcomplex binds NDUFAF3, NDUFAF4, TIMMDC1 to form Intermediate 1](#)

Literature references

McKenzie, M., Ryan, MT. (2010). Assembly factors of human mitochondrial complex I and their defects in disease. *IUBMB Life*, 62, 497-502. ↗

Andrews, B., Carroll, J., Ding, S., Fearnley, IM., Walker, JE. (2013). Assembly factors for the membrane arm of human complex I. *Proc. Natl. Acad. Sci. U.S.A.*, 110, 18934-9. ↗

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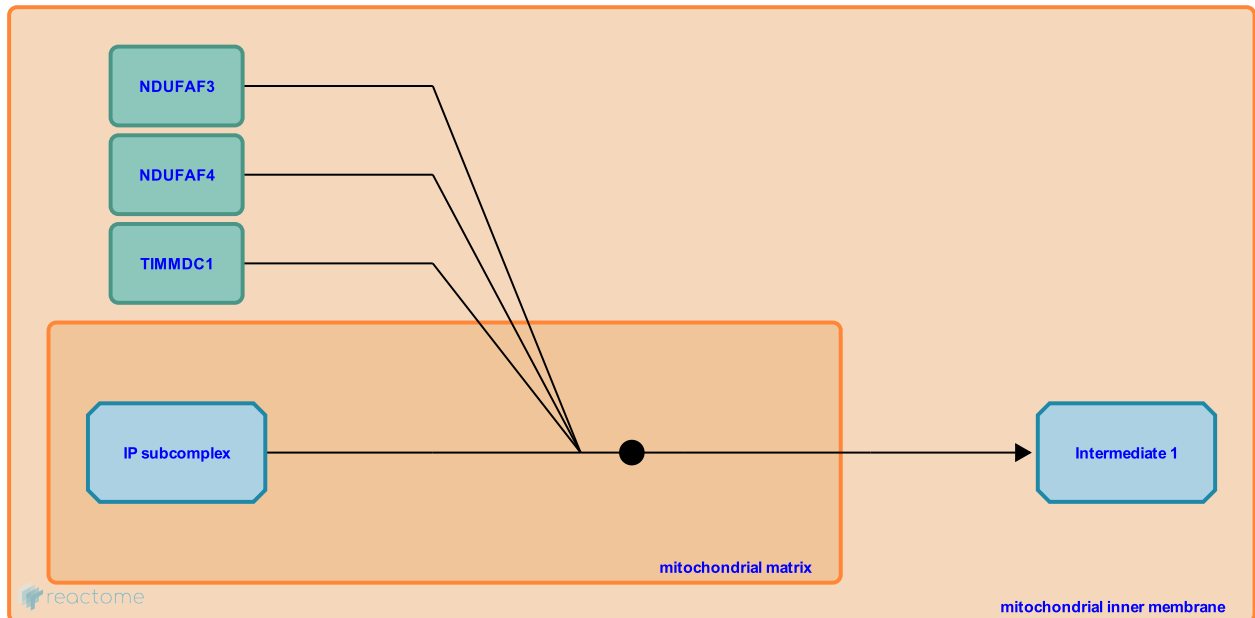
IP subcomplex binds NDUFAF3, NDUFAF4, TIMMDC1 to form Intermediate 1 [↗](#)

Location: [Complex I biogenesis](#)

Stable identifier: R-HSA-6799203

Type: binding

Compartments: mitochondrial matrix, mitochondrial inner membrane



Complex I assembly begins with the formation of a 315kDa subcomplex, centred around the core subunits NADH dehydrogenase [ubiquinone] iron-sulfur proteins 2 and 3 (NDUFS2 and NDUFS3) (Mckenzie & Ryan 2010, Mimaki et al. 2012, Andrews et al. 2013). NDUFS2 is thought to be bound to NDUFAF7 (Carilla-Latorre et al. 2010). Defects in NDUFS2 can cause mitochondrial complex I deficiency (MT-C1D; OMIM:252010), causing a wide range of clinical disorders, ranging from lethal neonatal disease to adult-onset neurodegenerative disorders (Loeffen et al. 2001). As an initial part of the 315kDa subcomplex, the subunits NDUFS7, S8 and A9, together with NDUFS2 and S3, form an evolutionarily conserved hydrogenase module as part of the Iron-Sulfur protein fraction (IP) subcomplex (termed Intermediate 1 here) (Mckenzie & Ryan 2010, Andrews et al. 2013).

Preceded by: [NDUF subunits bind to form the IP subcomplex](#)

Followed by: [Intermediate 1 binds HP subcomplex to form Intermediate 2](#)

Literature references

- Andrews, B., Carroll, J., Ding, S., Fearnley, IM., Walker, JE. (2013). Assembly factors for the membrane arm of human complex I. *Proc. Natl. Acad. Sci. U.S.A.*, 110, 18934-9. [↗](#)
- McKenzie, M., Ryan, MT. (2010). Assembly factors of human mitochondrial complex I and their defects in disease. *IUBMB Life*, 62, 497-502. [↗](#)
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- Mimaki, M., Wang, X., McKenzie, M., Thorburn, DR., Ryan, MT. (2012). Understanding mitochondrial complex I assembly in health and disease. *Biochim. Biophys. Acta*, 1817, 851-62. [↗](#)
- Loeffen, J., Elpeleg, O., Smeitink, J., Smeets, R., Stöckler-Ipsiroglu, S., Mandel, H. et al. (2001). Mutations in the complex I NDUFS2 gene of patients with cardiomyopathy and encephalomyopathy. *Ann. Neurol.*, 49, 195-201. [↗](#)

Editions

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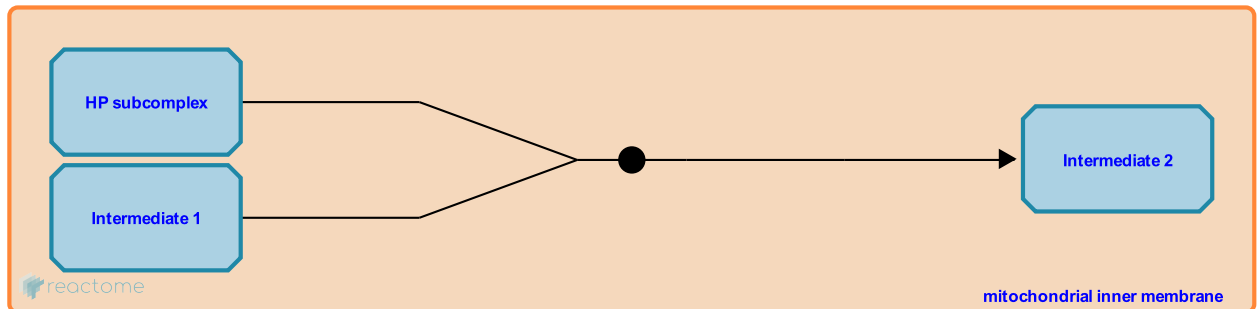
Intermediate 1 binds HP subcomplex to form Intermediate 2 [↗](#)

Location: [Complex I biogenesis](#)

Stable identifier: R-HSA-6799178

Type: binding

Compartments: mitochondrial inner membrane



The hydrophobic protein fraction (HP) is assembled with NDUFA3, 8, 9 and 13 amongst many others and anchored to the inner mitochondrial membrane by Intermediate 1 assembly factors NDUFAF3 (C3orf60), NDUFAF4 (C6orf66) and TIMMDC1 (C3orf1) to form Intermediate 2 (Mckenzie & Ryan 2010, Andrews et al. 2013).

Preceded by: [IP subcomplex binds NDUFAF3, NDUFAF4, TIMMDC1 to form Intermediate 1](#)

Followed by: [Intermediate 2 binds MT-ND1:NDUFAF5:NDUFAF6 to form a 315kDa subcomplex](#)

Literature references

Andrews, B., Carroll, J., Ding, S., Fearnley, IM., Walker, JE. (2013). Assembly factors for the membrane arm of human complex I. *Proc. Natl. Acad. Sci. U.S.A.*, 110, 18934-9. [↗](#)

McKenzie, M., Ryan, MT. (2010). Assembly factors of human mitochondrial complex I and their defects in disease. *IUBMB Life*, 62, 497-502. [↗](#)

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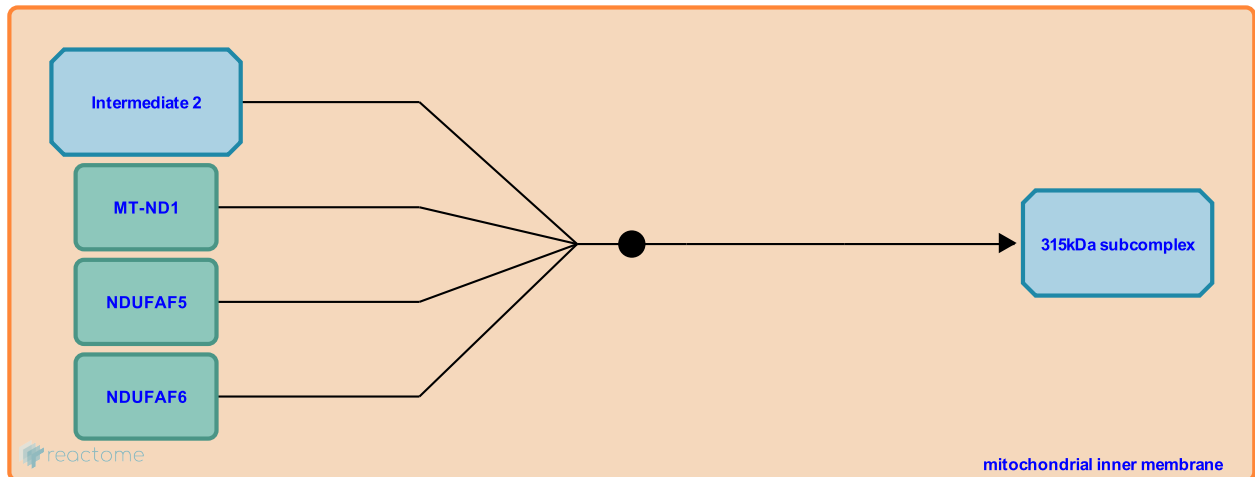
Intermediate 2 binds MT-ND1:NDUFAF5:NDUFAF6 to form a 315kDa subcomplex [↗](#)

Location: [Complex I biogenesis](#)

Stable identifier: R-HSA-6799191

Type: binding

Compartments: mitochondrial inner membrane



A complex I intermediate of 315kDa (reestimated from the original 400kDa) is formed centred around the core subunits NADH dehydrogenase [ubiquinone] iron-sulfur proteins 2 and 3 (NDUFS2 and NDUFS3) with other complex I subunits and assembly factor subunits (forming IP and HP subcomplexes). The IP subcomplex is anchored to the inner mitochondrial membrane by NADH-ubiquinone oxidoreductase chain 1 (MT-ND1) (together with NDUFAF5 and/or 6) (Mckenzie & Ryan 2010, Andrews et al. 2013).

Preceded by: [Intermediate 1 binds HP subcomplex to form Intermediate 2](#)

Followed by: [ND2, ND3, ND6, NDUFB6 bind the MCIA complex to form a 370kDa subcomplex](#)

Literature references

Andrews, B., Carroll, J., Ding, S., Fearnley, IM., Walker, JE. (2013). Assembly factors for the membrane arm of human complex I. *Proc. Natl. Acad. Sci. U.S.A.*, 110, 18934-9. [↗](#)

McKenzie, M., Ryan, MT. (2010). Assembly factors of human mitochondrial complex I and their defects in disease. *IUBMB Life*, 62, 497-502. [↗](#)

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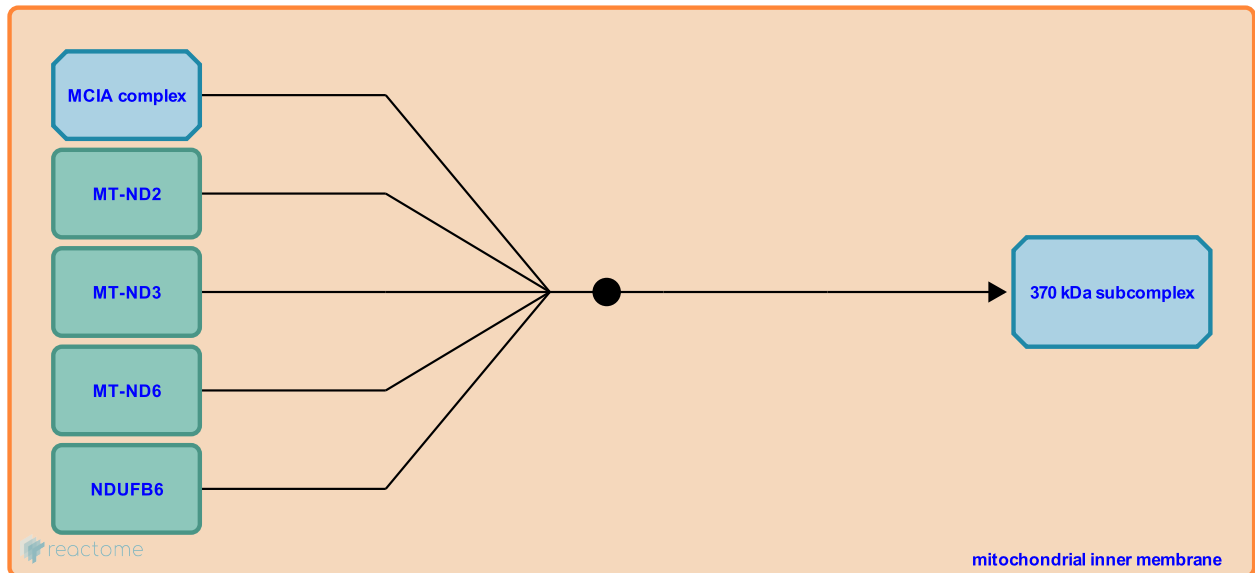
ND2, ND3, ND6, NDUFB6 bind the MCIA complex to form a 370kDa subcomplex ↗

Location: [Complex I biogenesis](#)

Stable identifier: R-HSA-6799199

Type: binding

Compartments: mitochondrial inner membrane



Membrane arm subunits MT-ND2, 3 and 6 and NDUFB6 associate with the assembly factors TMEM126B, NDUFAF1, ECSIT and ACAD9 (which form the MCIA complex) forming a 370kDa subcomplex (Mckenzie & Ryan 2010, Andrews et al. 2013).

Preceded by: [Intermediate 2 binds MT-ND1:NDUFAF5:NDUFAF6 to form a 315kDa subcomplex](#)

Followed by: [The 315kDa subcomplex binds the 370kDa subcomplex to form the 550kDa complex](#)

Literature references

Andrews, B., Carroll, J., Ding, S., Fearnley, IM., Walker, JE. (2013). Assembly factors for the membrane arm of human complex I. *Proc. Natl. Acad. Sci. U.S.A.*, 110, 18934-9. ↗

McKenzie, M., Ryan, MT. (2010). Assembly factors of human mitochondrial complex I and their defects in disease. *IUBMB Life*, 62, 497-502. ↗

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The 315kDa subcomplex binds the 370kDa subcomplex to form the 550kDa complex

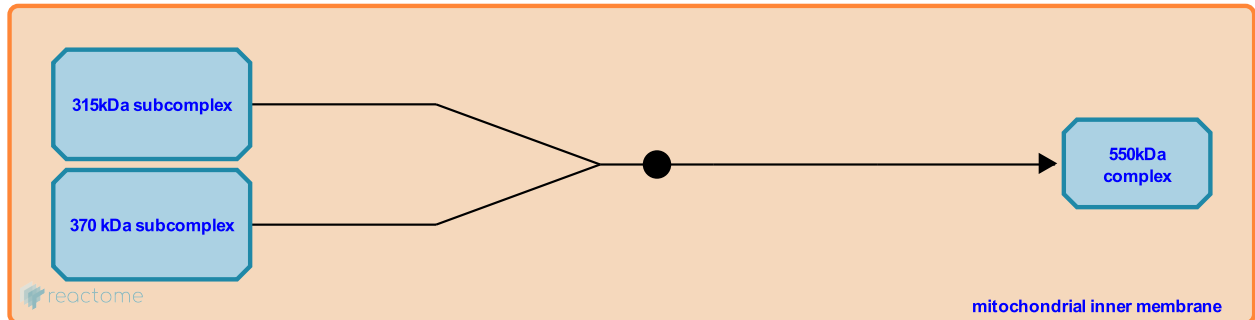


Location: [Complex I biogenesis](#)

Stable identifier: R-HSA-6799202

Type: binding

Compartments: mitochondrial inner membrane



The 315kDa and 370kDa subcomplexes associate to form a 550kDa complex (Mckenzie & Ryan 2010, Andrews et al. 2013).

Preceded by: [ND2, ND3, ND6, NDUFB6 bind the MCIA complex to form a 370kDa subcomplex](#)

Followed by: [ND4, ND5 bind the 550kDa complex to form the 815kDa complex](#)

Literature references

Andrews, B., Carroll, J., Ding, S., Fearnley, IM., Walker, JE. (2013). Assembly factors for the membrane arm of human complex I. *Proc. Natl. Acad. Sci. U.S.A.*, 110, 18934-9. [↗](#)

McKenzie, M., Ryan, MT. (2010). Assembly factors of human mitochondrial complex I and their defects in disease. *IUBMB Life*, 62, 497-502. [↗](#)

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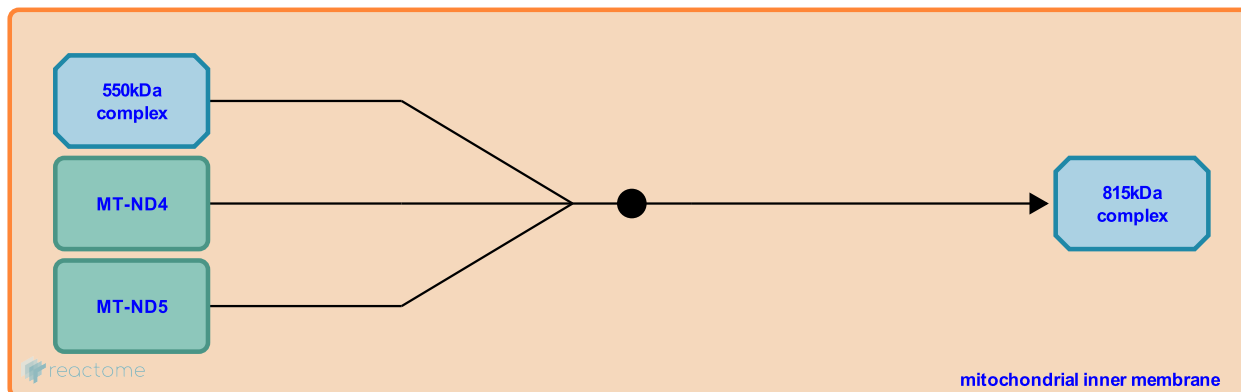
ND4, ND5 bind the 550kDa complex to form the 815kDa complex ↗

Location: [Complex I biogenesis](#)

Stable identifier: R-HSA-6799197

Type: binding

Compartments: mitochondrial inner membrane



Distal components of the membrane arm MT-ND4 and 5 associate with the 550kDa complex to form the 815kDa complex (McKenzie & Ryan 2010, Andrews et al. 2013).

Preceded by: [The 315kDa subcomplex binds the 370kDa subcomplex to form the 550kDa complex](#)

Followed by: [Peripheral arm subunits bind the 815kDa complex to form a 980kDa complex](#)

Literature references

Andrews, B., Carroll, J., Ding, S., Fearnley, IM., Walker, JE. (2013). Assembly factors for the membrane arm of human complex I. *Proc. Natl. Acad. Sci. U.S.A.*, 110, 18934-9. ↗

McKenzie, M., Ryan, MT. (2010). Assembly factors of human mitochondrial complex I and their defects in disease. *IUBMB Life*, 62, 497-502. ↗

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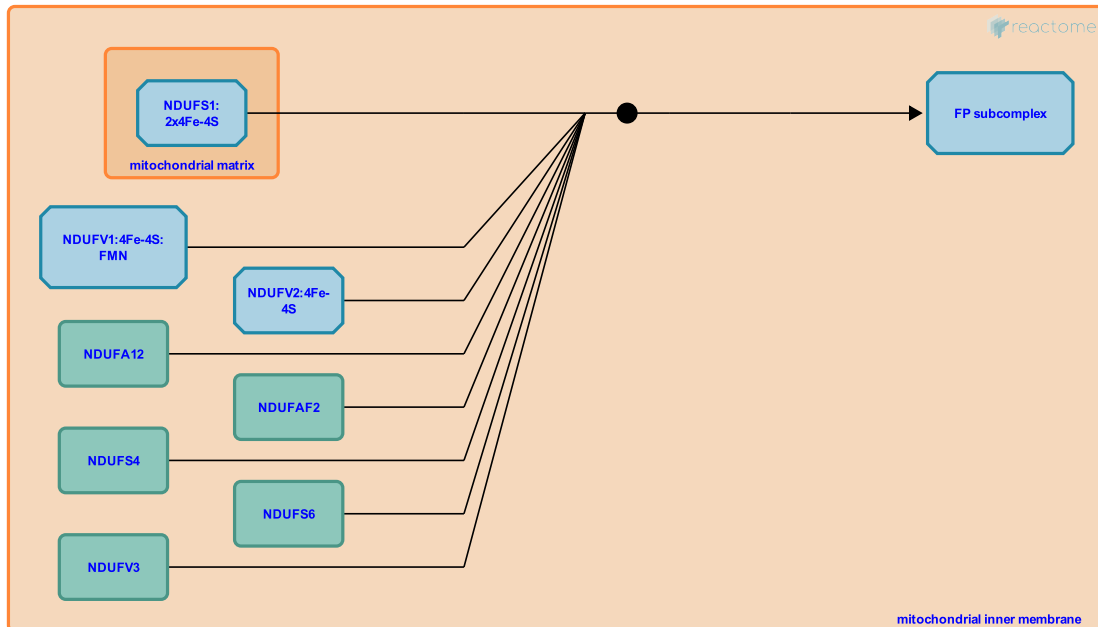
NDUF subunits bind to form the FP subcomplex ↗

Location: [Complex I biogenesis](#)

Stable identifier: R-HSA-6800870

Type: binding

Compartments: mitochondrial inner membrane, mitochondrial matrix



Subunits NDUFV1, NDUFV2, NDUFV3, NDUFV4, NDUFV5, NDUFV6 and the assembly factor NDUFV2 comprises the peripheral arm, called the flavoprotein (FP) subcomplex (Mimaki et al. 2012).

Preceded by: [NUBPL transfers 4Fe-4S to Complex I subunits](#), [NUBPL transfers 4Fe-4S to NDUFV1, V2](#)

Followed by: [Peripheral arm subunits bind the 815kDa complex to form a 980kDa complex](#)

Literature references

Mimaki, M., Wang, X., McKenzie, M., Thorburn, DR., Ryan, MT. (2012). Understanding mitochondrial complex I assembly in health and disease. *Biochim. Biophys. Acta*, 1817, 851-62. ↗

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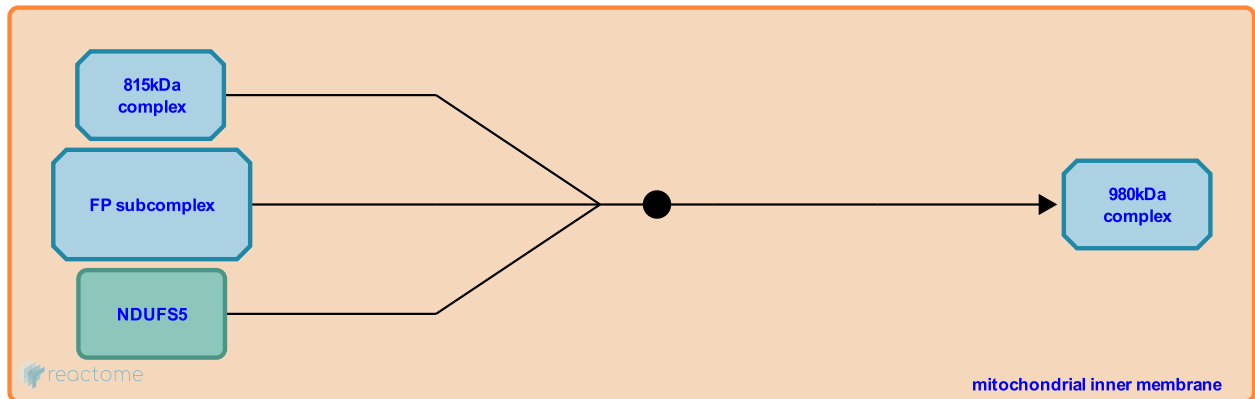
Peripheral arm subunits bind the 815kDa complex to form a 980kDa complex ↗

Location: [Complex I biogenesis](#)

Stable identifier: R-HSA-6799179

Type: binding

Compartments: mitochondrial inner membrane



Subunits NDUFA12, NDUFS1, 4, 6, NDUFV1, 2 and 3 with the assembly factor NDUFAF2 comprises the peripheral arm, called the flavoprotein (FP) subcomplex. In addition, remaining subunits such as NDUFS5 join here (Mimaki et al. 2012).

Preceded by: [ND4, ND5 bind the 550kDa complex to form the 815kDa complex](#), [NDUF subunits bind to form the FP subcomplex](#)

Followed by: [The MCIA complex, NDUFAF2-7 all dissociate from the 980kDa complex, resulting in Complex I](#)

Literature references

Mimaki, M., Wang, X., McKenzie, M., Thorburn, DR., Ryan, MT. (2012). Understanding mitochondrial complex I assembly in health and disease. *Biochim. Biophys. Acta*, 1817, 851-62. ↗

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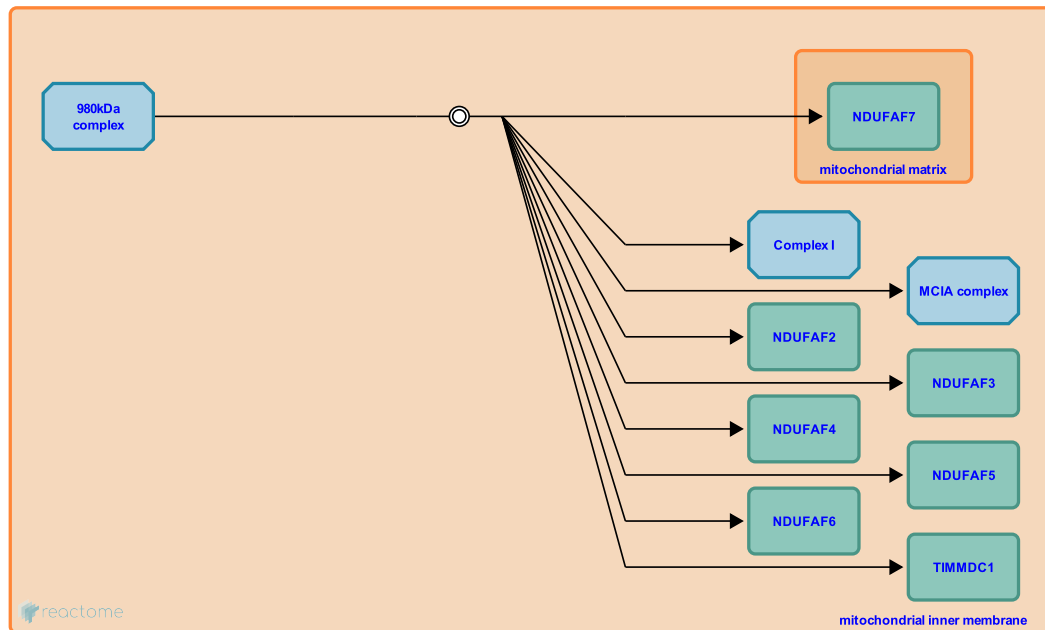
The MCIA complex, NDUFAF2-7 all dissociate from the 980kDa complex, resulting in Complex I ↗

Location: [Complex I biogenesis](#)

Stable identifier: R-HSA-6799196

Type: dissociation

Compartments: mitochondrial inner membrane



In the last step, the MCIA complex and its assembly factors (NDUFAF2-7, TIMMDC1) dissociate from the 980kDa complex to leave mature Complex I (McKenzie & Ryan 2010, Andrews et al. 2013).

Preceded by: [Peripheral arm subunits bind the 815kDa complex to form a 980kDa complex](#)

Literature references

Andrews, B., Carroll, J., Ding, S., Fearnley, IM., Walker, JE. (2013). Assembly factors for the membrane arm of human complex I. *Proc. Natl. Acad. Sci. U.S.A.*, 110, 18934-9. ↗

McKenzie, M., Ryan, MT. (2010). Assembly factors of human mitochondrial complex I and their defects in disease. *IUBMB Life*, 62, 497-502. ↗

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