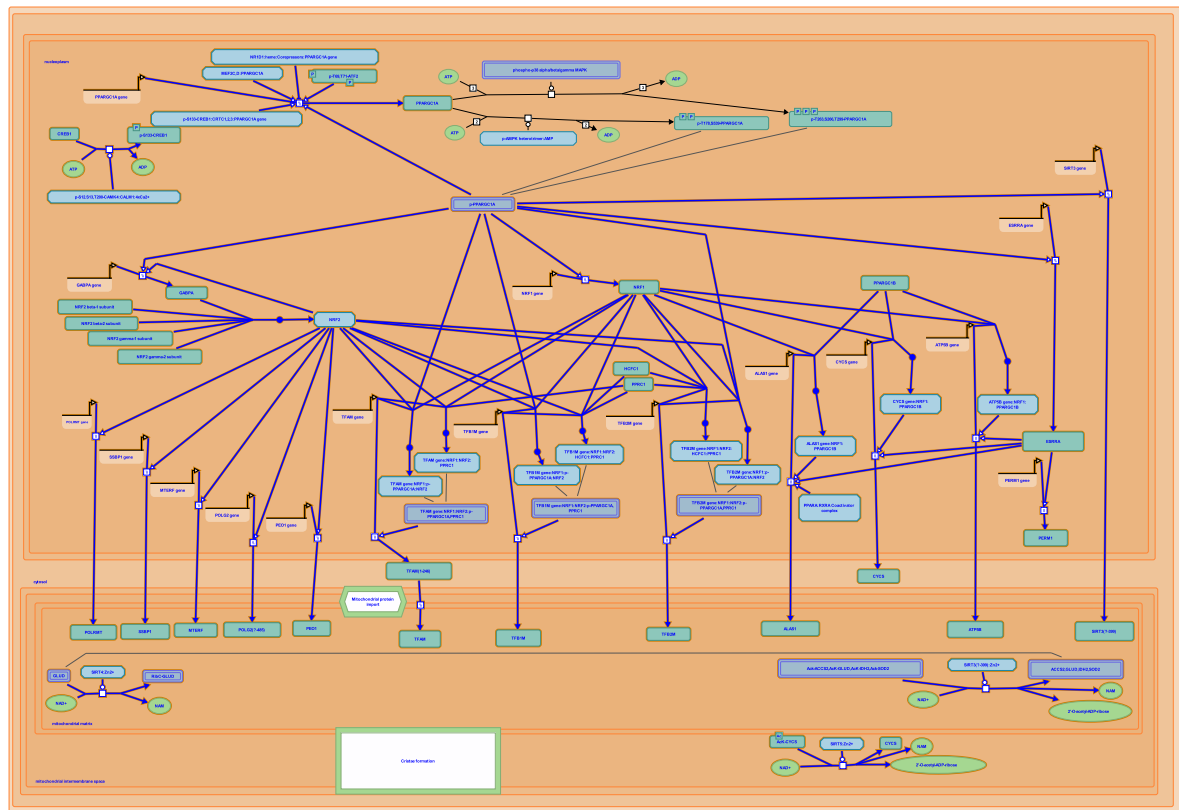


Transcriptional activation of mitochondrial biogenesis



Castagnoli, L., Gillespie, ME., Haigis, M., Hansen, KB., Jassal, B., Jupe, S., Kralli, A., Le Novere, N., Lezza, AM., Mahajan, SS., May, B., Orlic-Milacic, M., Somers, J., Tukey, D., Yi, F.

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

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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the [Reactome Textbook](https://reactome.org/textbook/).

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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- Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics*, 33, 3461-3467. [↗](#)
- Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res*, 46, D649-D655. [↗](#)
- 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. [↗](#)

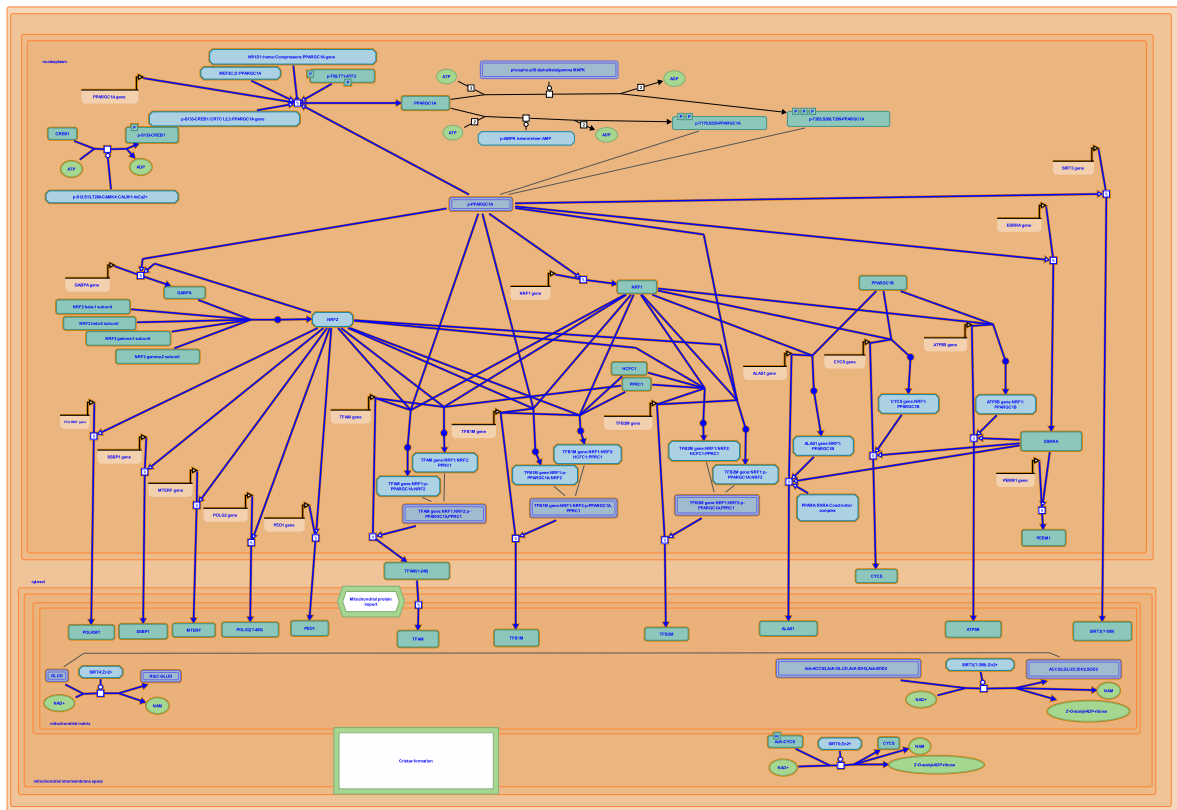
Reactome database release: 88

This document contains 1 pathway and 32 reactions ([see Table of Contents](#))

Transcriptional activation of mitochondrial biogenesis ↗

Stable identifier: R-HSA-2151201

Compartments: cytosol, nucleoplasm, mitochondrial matrix



reactome

Phosphorylated PPARGC1A (PGC-1alpha) does not bind DNA directly but instead interacts with other transcription factors, notably NRF1 and NRF2 (via HCF1). NRF1 and NRF2 together with PPARGC1A activate the transcription of nuclear-encoded, mitochondrially targeted proteins such as TFB2M, TFB1M, and TFAM. PGC-1beta and PPRC appear to act similarly to PGC-1alpha but have not been as well studied. Transcription of PPARGC1A itself is upregulated by CREB1 (in response to calcium), MEF2C/D, ATF2, and PPARGC1A. Transcription of PPARGC1A is repressed by NR1D1 (REV-ERBA).

Literature references

- Kralli, A., Hock, MB. (2009). Transcriptional control of mitochondrial biogenesis and function. *Annu Rev Physiol*, 71, 177-203. ↗
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- Scarpulla, RC. (2011). Metabolic control of mitochondrial biogenesis through the PGC-1 family regulatory network. *Biochim Biophys Acta*, 1813, 1269-78. ↗
- Scarpulla, RC., Kelly, DP., Vega, RB. (2012). Transcriptional integration of mitochondrial biogenesis. *Trends Endocrinol. Metab.*, 23, 459-66. ↗

Editions

2012-02-27	Authored, Edited	May, B.
2013-12-07	Reviewed	Lezza, AM.

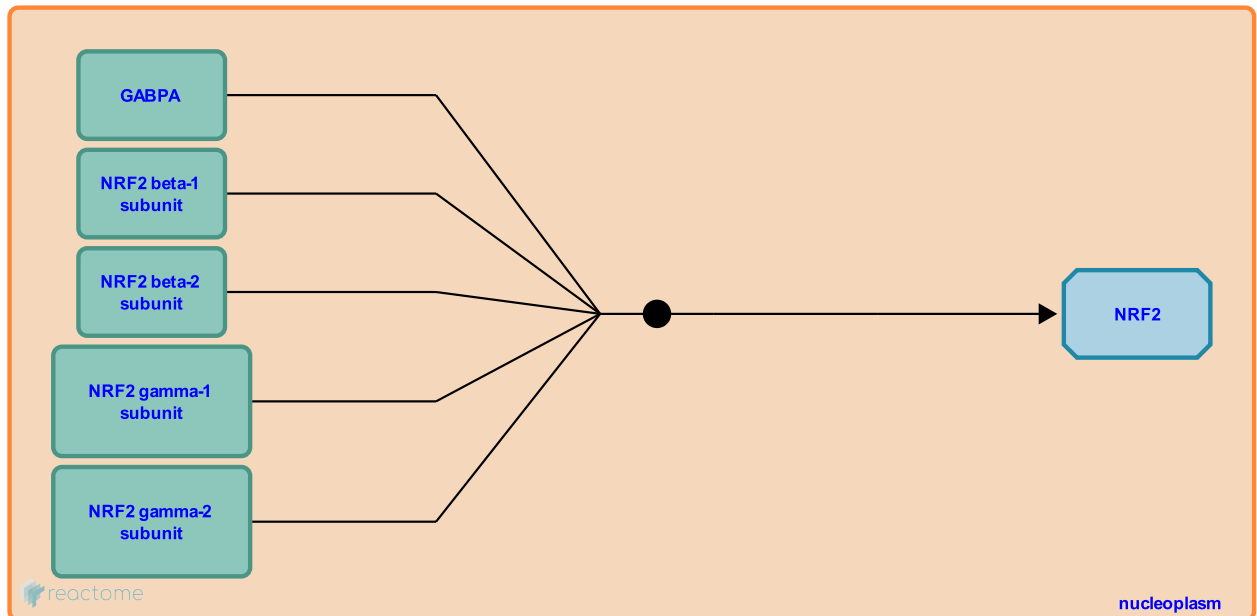
Formation of NRF2 [↗](#)

Location: [Transcriptional activation of mitochondrial biogenesis](#)

Stable identifier: R-HSA-1592240

Type: binding

Compartments: nucleoplasm



Five subunits (alpha, beta-1, beta-2, gamma-1, gamma-2) assemble to form the DNA-binding transcription factor NRF2 (Gugneja et al. 1995).

Preceded by: [Expression of GABPA \(NRF2 alpha subunit\)](#)

Followed by: [Expression of PEO1](#), [Expression of POLG2](#), [NRF1:p-PPARGC1A](#), [NRF2 bind the TFB1M promoter](#), [Expression of POLRMT](#), [Expression of SSBP1](#), [NRF1:p-PPARGC1A](#), [NRF2 bind the TFB2M promoter](#), [Expression of mTERF](#), [NRF1](#), [PPRC1:HCFC1:NRF2 bind the TFB1M promoter](#), [NRF1](#), [PPRC1:HCFC1:NRF2 bind the TFB2M promoter](#)

Literature references

Virbasius, JV., Gugneja, S., Scarpulla, RC. (1995). Four structurally distinct, non-DNA-binding subunits of human nuclear respiratory factor 2 share a conserved transcriptional activation domain. *Mol Cell Biol*, 15, 102-11. [↗](#)

Editions

2011-08-20	Authored, Edited	May, B.
2013-12-07	Reviewed	Lezza, AM.

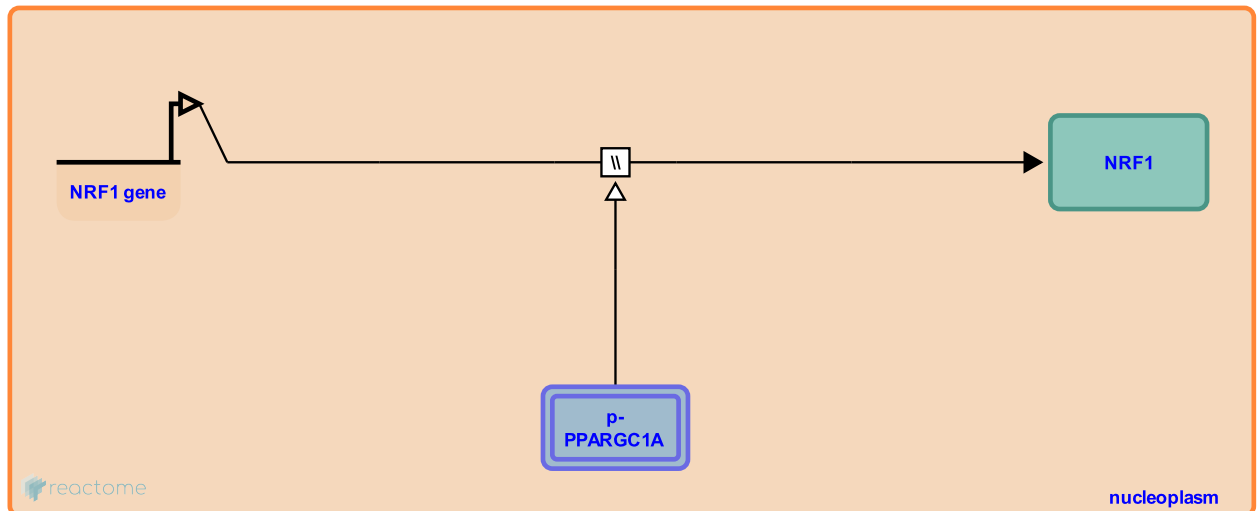
Expression of NRF1 [↗](#)

Location: [Transcriptional activation of mitochondrial biogenesis](#)

Stable identifier: R-HSA-1592242

Type: omitted

Compartments: nucleoplasm



The NRF1 gene is transcribed to yield mRNA and the mRNA is translated to yield protein. NRF1 protein is located in the nucleus where it regulates transcription.

Followed by: [NRF1:p-PPARGC1A, NRF2 bind the TFB1M promoter](#), [NRF1:p-PPARGC1A, NRF2 bind the TFAM promoter](#), [NRF1:PPARGC1B binds the CYCS promoter](#), [NRF1:p-PPARGC1A, NRF2 bind the TFB2M promoter](#), [NRF1:PPARGC1B binds the ATP5B promoter](#), [NRF1, PPRC1, NRF2 bind the TFAM promoter](#), [NRF1:PPARGC1B binds the ALAS1 promoter](#)

Literature references

Gopalakrishnan, L., Scarpulla, RC. (1995). Structure, expression, and chromosomal assignment of the human gene encoding nuclear respiratory factor 1. *J Biol Chem*, 270, 18019-25. [↗](#)

Editions

2011-08-20	Authored, Edited	May, B.
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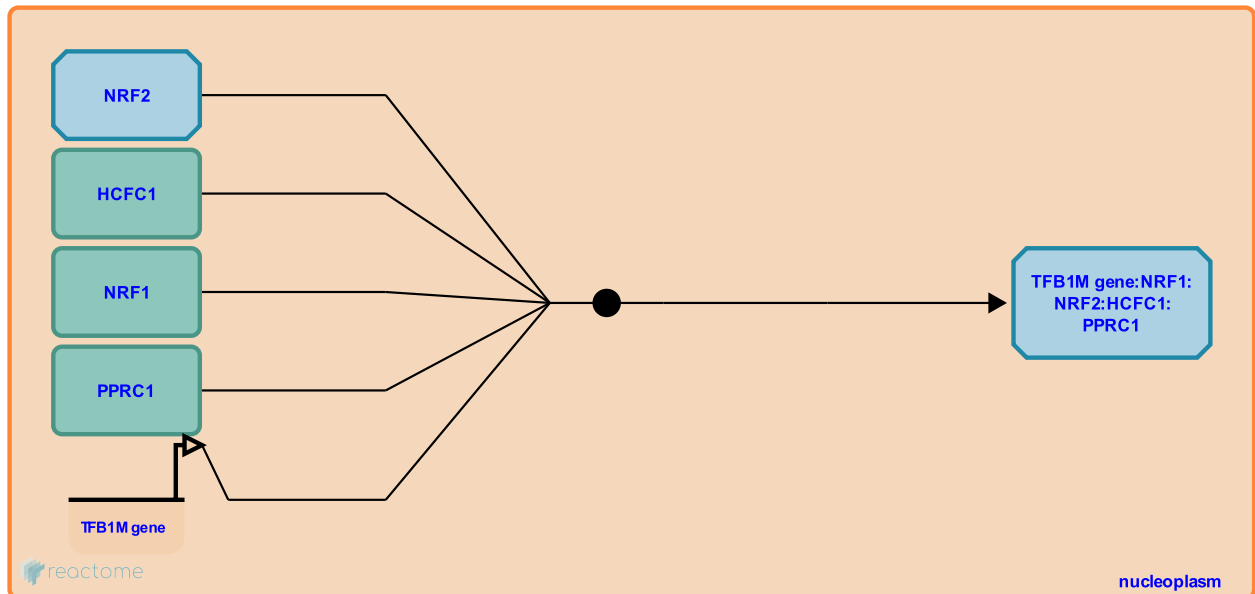
NRF1, PPRC1:HCFC1:NRF2 bind the TFB1M promoter ↗

Location: [Transcriptional activation of mitochondrial biogenesis](#)

Stable identifier: R-HSA-1592250

Type: binding

Compartments: nucleoplasm



Both PRC (PPRC1) and NRF2 bind HCF1 (Vercauteren et al. 2008). PRC, like PGC-1alpha, can coactivate NRF2 (Gleyzer et al. 2005).

Preceded by: [Formation of NRF2](#)

Followed by: [Expression of TFB1M](#)

Literature references

Gleyzer, N., Scarpulla, RC., Vercauteren, K. (2005). Control of mitochondrial transcription specificity factors (TFB1M and TFB2M) by nuclear respiratory factors (NRF-1 and NRF-2) and PGC-1 family coactivators. *Mol Cell Biol*, 25, 1354-66. ↗

Gleyzer, N., Scarpulla, RC., Vercauteren, K. (2008). PGC-1-related coactivator complexes with HCF-1 and NRF-2beta in mediating NRF-2(GABP)-dependent respiratory gene expression. *J Biol Chem*, 283, 12102-11. ↗

Editions

2011-08-20	Authored, Edited	May, B.
2013-12-07	Reviewed	Lezza, AM.

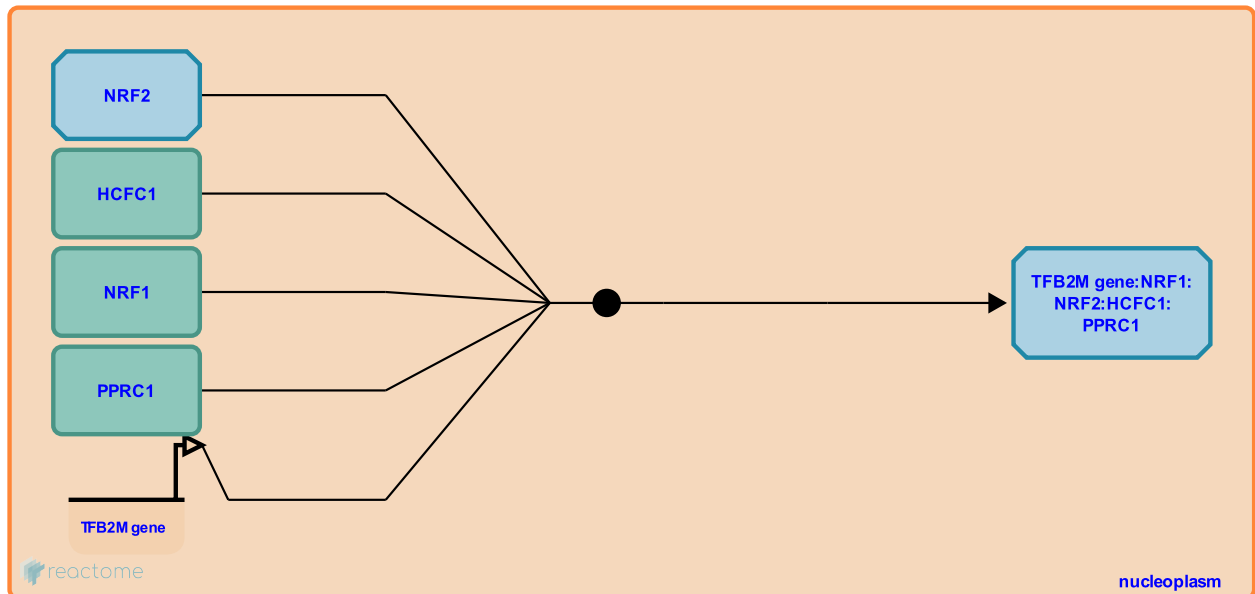
NRF1, PPRC1:HCFC1:NRF2 bind the TFB2M promoter ↗

Location: [Transcriptional activation of mitochondrial biogenesis](#)

Stable identifier: R-HSA-2466367

Type: binding

Compartments: nucleoplasm



Both PRC (PPRC1) and NRF2 bind HCF1 (Vercauteren et al. 2008). PRC, like PGC-1alpha, can coactivate NRF2 (Gleyzer et al. 2005).

Preceded by: [Formation of NRF2](#)

Followed by: [Expression of TFB2M](#)

Literature references

Gleyzer, N., Scarpulla, RC., Vercauteren, K. (2005). Control of mitochondrial transcription specificity factors (TFB1M and TFB2M) by nuclear respiratory factors (NRF-1 and NRF-2) and PGC-1 family coactivators. *Mol Cell Biol*, 25, 1354-66. ↗

Gleyzer, N., Scarpulla, RC., Vercauteren, K. (2008). PGC-1-related coactivator complexes with HCF-1 and NRF-2beta in mediating NRF-2(GABP)-dependent respiratory gene expression. *J Biol Chem*, 283, 12102-11. ↗

Editions

2011-08-20	Authored, Edited	May, B.
2013-12-07	Reviewed	Lezza, AM.

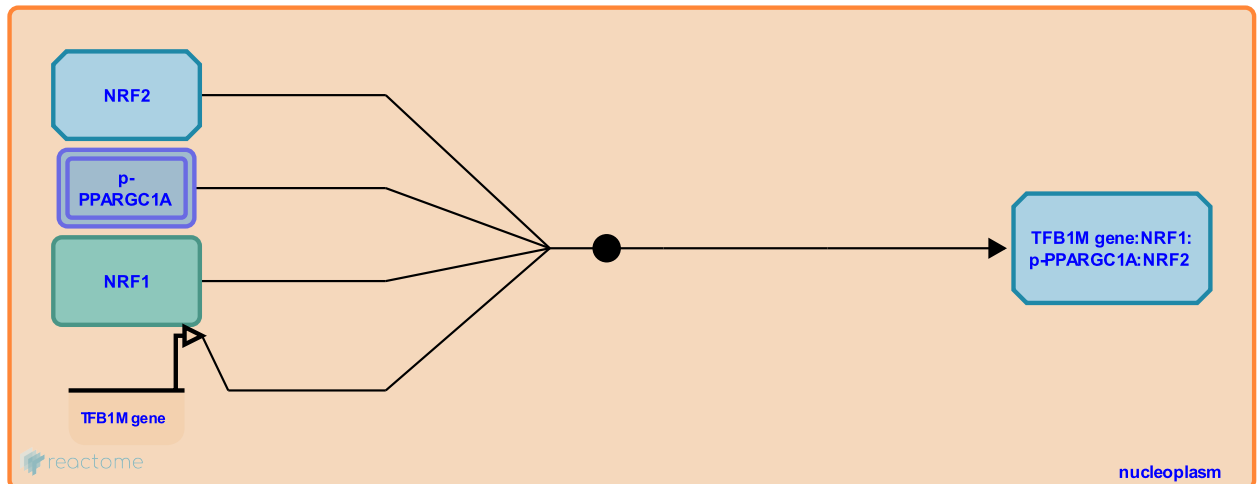
NRF1:p-PPARGC1A, NRF2 bind the TFB1M promoter ↗

Location: [Transcriptional activation of mitochondrial biogenesis](#)

Stable identifier: R-HSA-1592236

Type: binding

Compartments: nucleoplasm



PGC-1alpha (PPARGC1A) binds NRF1 and coactivates genes regulated by NRF1 (Gleyzer et al. 2005, Vercauteren et al. 2008, inferred from mouse in Wu et al. 1999).

Preceded by: [Expression of NRF1](#), [Formation of NRF2](#)

Followed by: [Expression of TFB1M](#)

Literature references

Spiegelman, BM., Cinti, S., Lowell, B., Wu, Z., Adelmant, G., Mootha, V. et al. (1999). Mechanisms controlling mitochondrial biogenesis and respiration through the thermogenic coactivator PGC-1. *Cell*, 98, 115-24. ↗

Gleyzer, N., Scarpulla, RC., Vercauteren, K. (2005). Control of mitochondrial transcription specificity factors (TFB1M and TFB2M) by nuclear respiratory factors (NRF-1 and NRF-2) and PGC-1 family coactivators. *Mol Cell Biol*, 25, 1354-66. ↗

Editions

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2013-12-07	Reviewed	Lezza, AM.

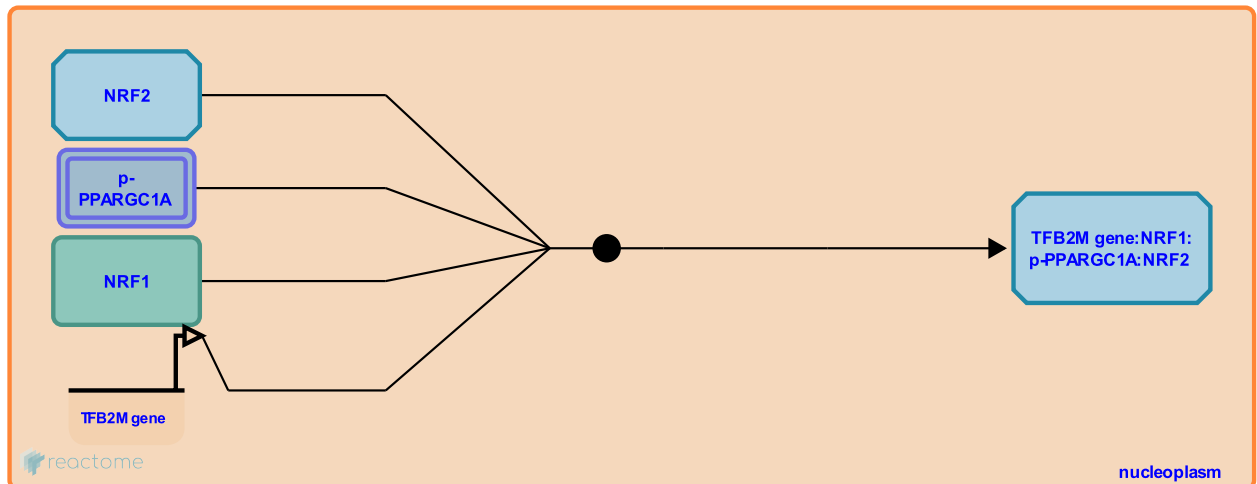
NRF1:p-PPARGC1A, NRF2 bind the TFB2M promoter ↗

Location: [Transcriptional activation of mitochondrial biogenesis](#)

Stable identifier: R-HSA-2466392

Type: binding

Compartments: nucleoplasm



PGC-1alpha (PPARGC1A) binds NRF1 and coactivates genes regulated by NRF1 (Gleyzer et al. 2005, Vercauteren et al. 2008, inferred from mouse in Wu et al. 1999).

Preceded by: [Expression of NRF1](#), [Formation of NRF2](#)

Followed by: [Expression of TFB2M](#)

Literature references

Spiegelman, BM., Cinti, S., Lowell, B., Wu, Z., Adelmant, G., Mootha, V. et al. (1999). Mechanisms controlling mitochondrial biogenesis and respiration through the thermogenic coactivator PGC-1. *Cell*, 98, 115-24. ↗

Gleyzer, N., Scarpulla, RC., Vercauteren, K. (2005). Control of mitochondrial transcription specificity factors (TFB1M and TFB2M) by nuclear respiratory factors (NRF-1 and NRF-2) and PGC-1 family coactivators. *Mol Cell Biol*, 25, 1354-66. ↗

Editions

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2013-12-07	Reviewed	Lezza, AM.

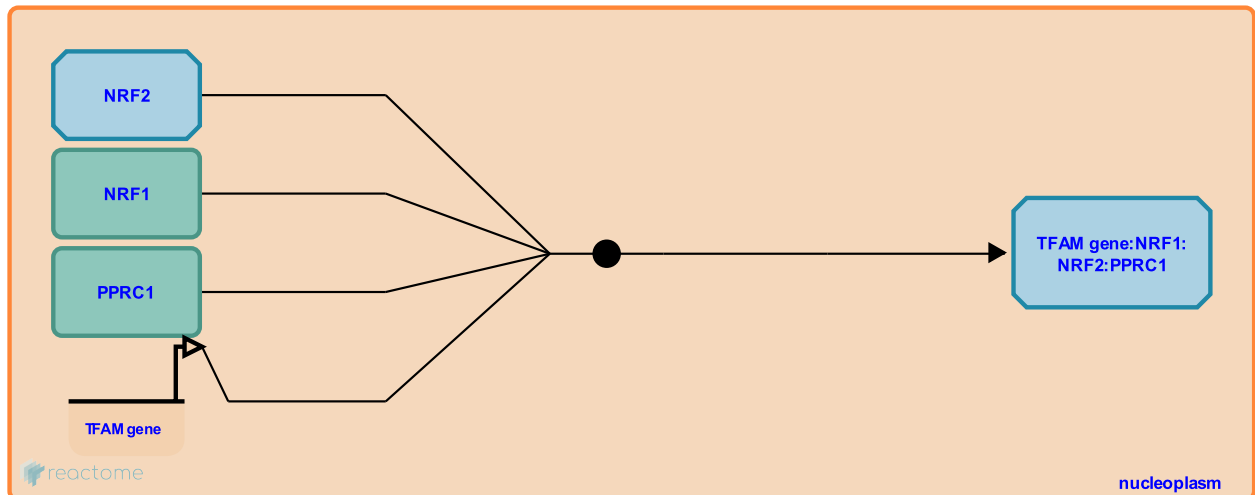
NRF1, PPRC1, NRF2 bind the TFAM promoter ↗

Location: [Transcriptional activation of mitochondrial biogenesis](#)

Stable identifier: R-HSA-1592249

Type: binding

Compartments: nucleoplasm



PPRC1 (PPRC1) binds NRF1 and coactivates genes regulated by NRF1 (Andersson and Scarpulla 2001, Vercauteren et al. 2008).

Preceded by: [Expression of NRF1](#)

Followed by: [Expression of TFAM](#)

Literature references

Andersson, U., Scarpulla, RC. (2001). Pgc-1-related coactivator, a novel, serum-inducible coactivator of nuclear respiratory factor 1-dependent transcription in mammalian cells. *Mol Cell Biol*, 21, 3738-49. ↗

Gleyzer, N., Scarpulla, RC., Vercauteren, K. (2008). PGC-1-related coactivator complexes with HCF-1 and NRF-2beta in mediating NRF-2(GABP)-dependent respiratory gene expression. *J Biol Chem*, 283, 12102-11. ↗

Editions

2011-08-20	Authored, Edited	May, B.
2013-12-07	Reviewed	Lezza, AM.

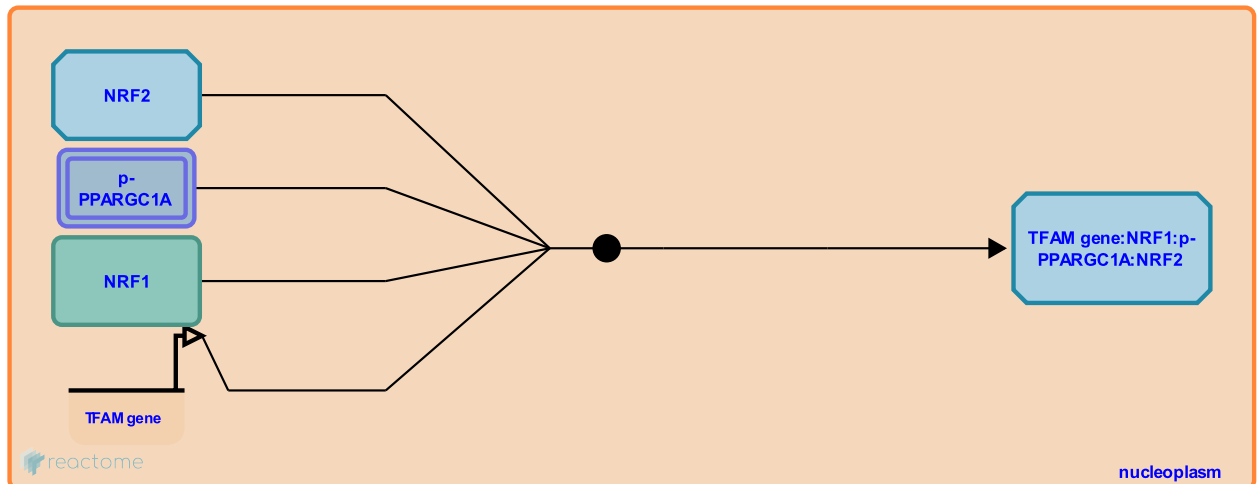
NRF1:p-PPARGC1A, NRF2 bind the TFAM promoter ↗

Location: [Transcriptional activation of mitochondrial biogenesis](#)

Stable identifier: R-HSA-2466391

Type: binding

Compartments: nucleoplasm



PRC (PPRC1) binds NRF1 and coactivates genes regulated by NRF1 (Andersson and Scarpulla 2001, Vercauteren et al. 2008).

Preceded by: [Expression of NRF1](#)

Followed by: [Expression of TFAM](#)

Literature references

Andersson, U., Scarpulla, RC. (2001). Pgc-1-related coactivator, a novel, serum-inducible coactivator of nuclear respiratory factor 1-dependent transcription in mammalian cells. *Mol Cell Biol*, 21, 3738-49. ↗

Gleyzer, N., Scarpulla, RC., Vercauteren, K. (2008). PGC-1-related coactivator complexes with HCF-1 and NRF-2beta in mediating NRF-2(GABP)-dependent respiratory gene expression. *J Biol Chem*, 283, 12102-11. ↗

Editions

2011-08-20	Authored, Edited	May, B.
2013-12-07	Reviewed	Lezza, AM.

NRF1:PPARGC1B binds the ALAS1 promoter ↗

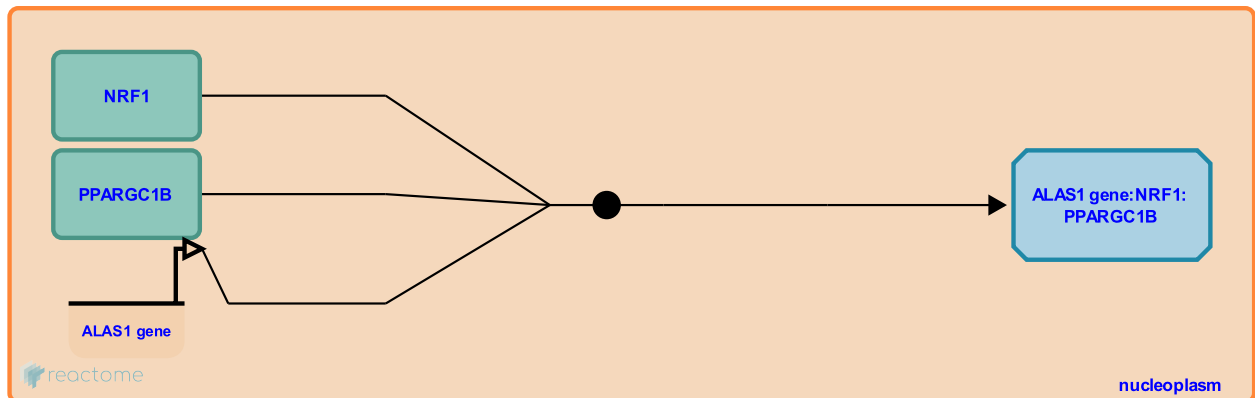
Location: [Transcriptional activation of mitochondrial biogenesis](#)

Stable identifier: R-HSA-1592245

Type: binding

Compartments: nucleoplasm

Inferred from: [Formation of Nrf1:Pgc-1beta \(Ppargc1b\) \(Mus musculus\)](#)



As inferred from mouse, PGC-1beta (PPARGC1B) binds NRF1 and coactivates genes regulated by NRF1.

Preceded by: [Expression of NRF1](#)

Followed by: [Expression of ALAS1](#)

Editions

2011-08-20	Authored, Edited	May, B.
2013-12-07	Reviewed	Lezza, AM.

NRF1:PPARGC1B binds the ATP5B promoter ↗

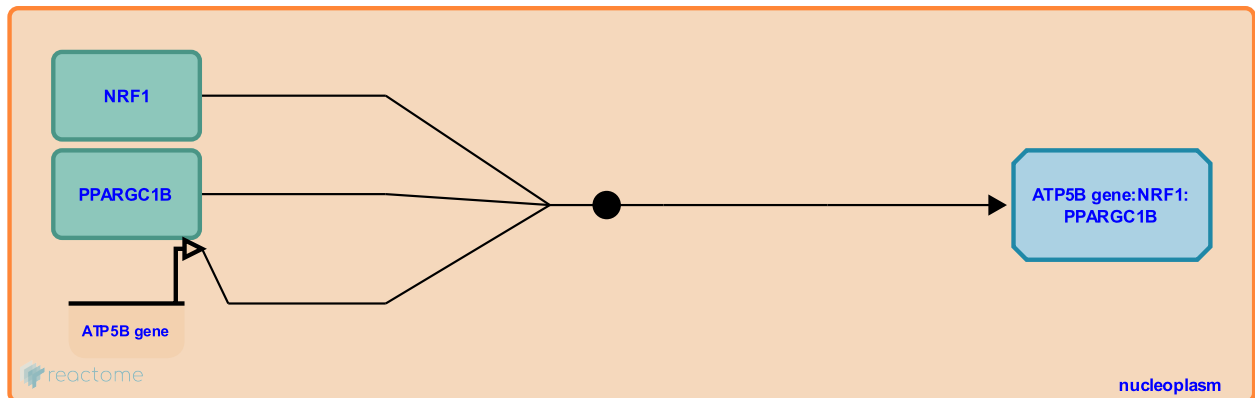
Location: [Transcriptional activation of mitochondrial biogenesis](#)

Stable identifier: R-HSA-2466369

Type: binding

Compartments: nucleoplasm

Inferred from: [Formation of Nrf1:Pgc-1beta \(Ppargc1b\) \(Mus musculus\)](#)



As inferred from mouse, PGC-1beta (PPARGC1B) binds NRF1 and coactivates genes regulated by NRF1.

Preceded by: [Expression of NRF1](#)

Followed by: [Expression of ATP5B](#)

Editions

2011-08-20	Authored, Edited	May, B.
2013-12-07	Reviewed	Lezza, AM.

NRF1:PPARGC1B binds the CYCS promoter ↗

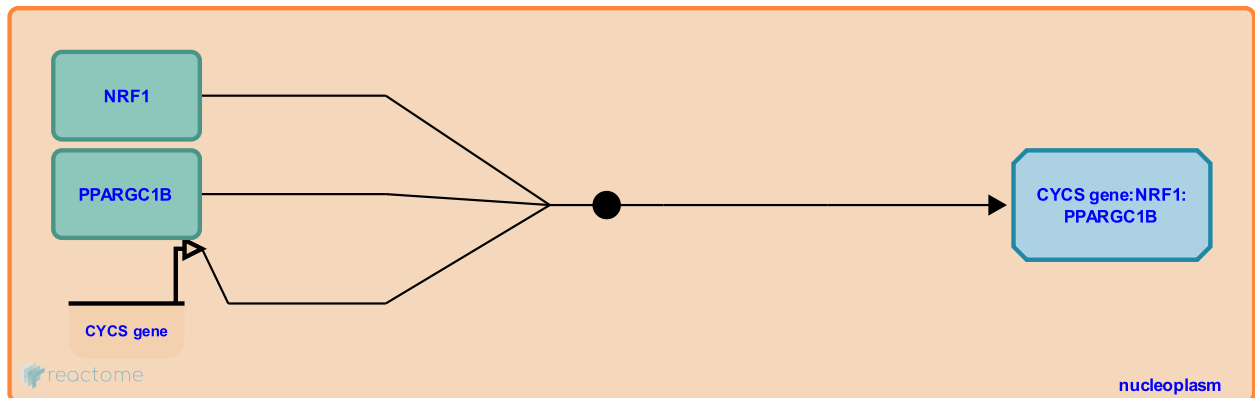
Location: [Transcriptional activation of mitochondrial biogenesis](#)

Stable identifier: R-HSA-2466370

Type: binding

Compartments: nucleoplasm

Inferred from: [Formation of Nrf1:Pgc-1beta \(Ppargc1b\) \(Mus musculus\)](#)



As inferred from mouse, PGC-1beta (PPARGC1B) binds NRF1 and coactivates genes regulated by NRF1.

Preceded by: [Expression of NRF1](#)

Followed by: [Expression of CYCS](#)

Editions

2011-08-20	Authored, Edited	May, B.
2013-12-07	Reviewed	Lezza, AM.

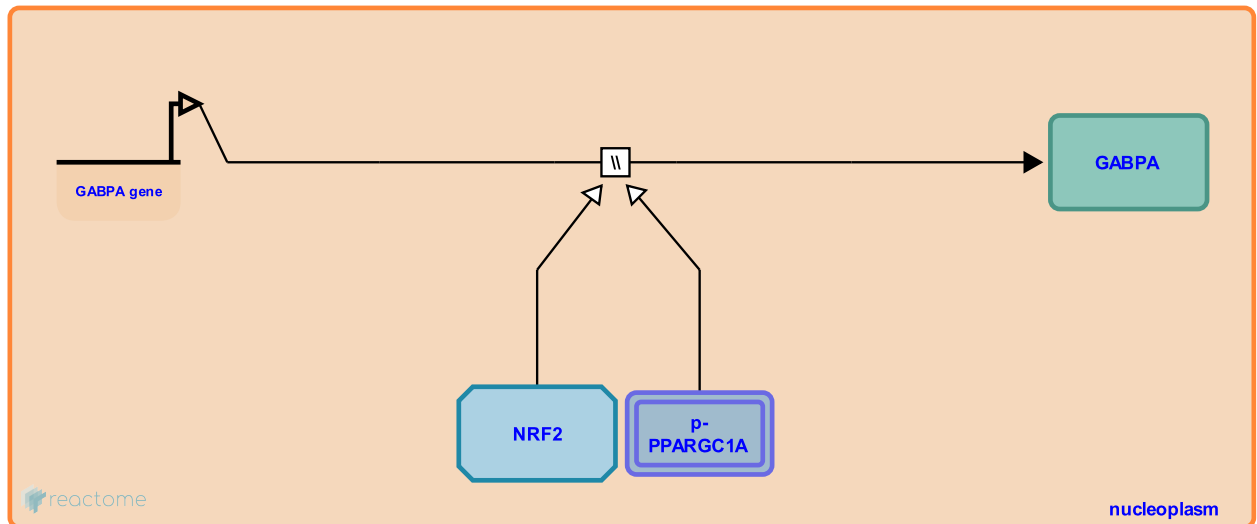
Expression of GABPA (NRF2 alpha subunit) ↗

Location: [Transcriptional activation of mitochondrial biogenesis](#)

Stable identifier: R-HSA-1592234

Type: omitted

Compartments: nucleoplasm



As inferred from mouse, NRF2 binds the promoter of the GABPA (NRF2 alpha subunit) gene and enhances transcription.

The GABPA (NRF2 alpha subunit) gene is transcribed to yield mRNA and the mRNA is translated to yield protein. Two subunits of GABPA bind two subunits of GABPB1 to form Nuclear respiratory factor 2 (NRF2).

Followed by: [Formation of NRF2](#)

Literature references

Virbasius, JV., Gugneja, S., Scarpulla, RC. (1995). Four structurally distinct, non-DNA-binding subunits of human nuclear respiratory factor 2 share a conserved transcriptional activation domain. *Mol Cell Biol*, 15, 102-11. ↗

Editions

2011-08-20	Authored, Edited	May, B.
2013-12-07	Reviewed	Lezza, AM.

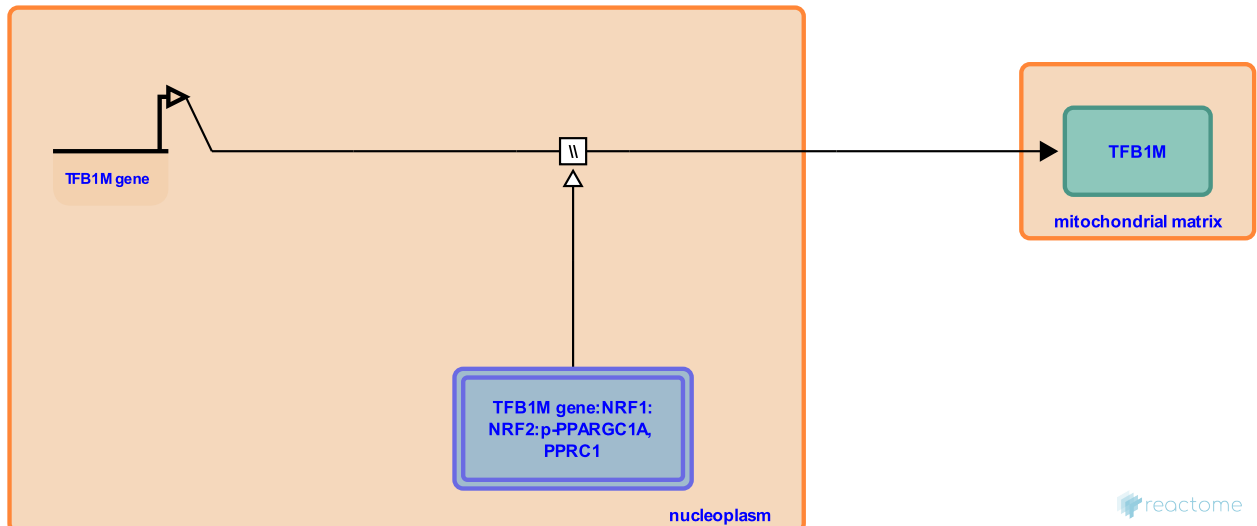
Expression of TFB1M ↗

Location: [Transcriptional activation of mitochondrial biogenesis](#)

Stable identifier: R-HSA-1592232

Type: omitted

Compartments: nucleoplasm, mitochondrial matrix



The TFB1M gene is transcribed to yield mRNA and the mRNA is translated to yield precursor protein in the cytosol (McCulloch et al. 2002, Gleyzer et al. 2005, Vercauteren et al. 2008, Cotney et al. 2009). The TFB1M precursor is then imported into the mitochondrial matrix where it acts as both a 12S RNA methylase and a DNA-binding transcription factor (inferred from mouse in Metodiev et al. 2009).

Preceded by: [NRF1:p-PPARGC1A, NRF2 bind the TFB1M promoter](#), [NRF1, PPRC1:HCFC1:NRF2 bind the TFB1M promoter](#)

Literature references

- Gleyzer, N., Scarpulla, RC., Vercauteren, K. (2005). Control of mitochondrial transcription specificity factors (TFB1M and TFB2M) by nuclear respiratory factors (NRF-1 and NRF-2) and PGC-1 family coactivators. *Mol Cell Biol*, 25, 1354-66. ↗
- McCulloch, V., Seidel-Rogol, BL., Shadel, GS. (2002). A human mitochondrial transcription factor is related to RNA adenine methyltransferases and binds S-adenosylmethionine. *Mol Cell Biol*, 22, 1116-25. ↗
- McKay, SE., Shadel, GS., Cotney, J. (2009). Elucidation of separate, but collaborative functions of the rRNA methyltransferase-related human mitochondrial transcription factors B1 and B2 in mitochondrial biogenesis reveals new insight into maternally inherited deafness. *Hum. Mol. Genet.*, 18, 2670-82. ↗
- Gleyzer, N., Scarpulla, RC., Vercauteren, K. (2008). PGC-1-related coactivator complexes with HCF-1 and NRF-2beta in mediating NRF-2(GABP)-dependent respiratory gene expression. *J Biol Chem*, 283, 12102-11. ↗
- Park, CB., Lesko, N., Cámara, Y., Larsson, NG., Gustafsson, CM., Hultenby, K. et al. (2009). Methylation of 12S rRNA is necessary for in vivo stability of the small subunit of the mammalian mitochondrial ribosome. *Cell Metab.*, 9, 386-97. ↗

Editions

2011-08-20	Authored, Edited	May, B.
2013-12-07	Reviewed	Lezza, AM.

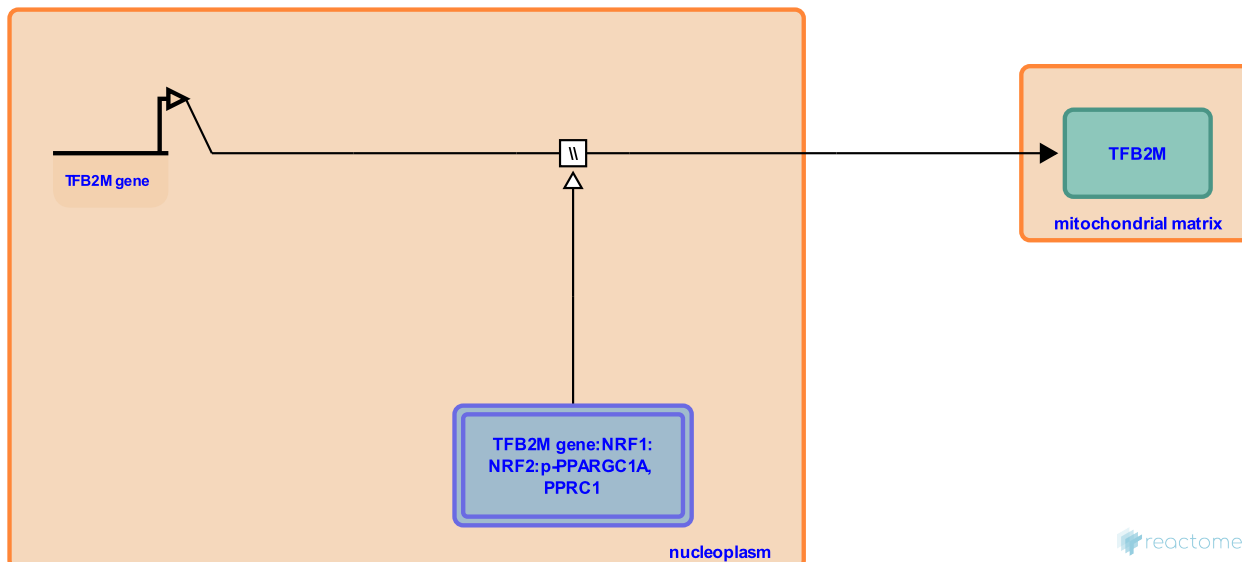
Expression of TFB2M ↗

Location: [Transcriptional activation of mitochondrial biogenesis](#)

Stable identifier: R-HSA-1592252

Type: omitted

Compartments: nucleoplasm, mitochondrial matrix



The TFB2M gene is transcribed to yield mRNA and the mRNA is translated to yield protein. The TFB2M precursor is then imported into the mitochondrial matrix where it acts as both a 12S RNA methylase and a DNA-binding transcription factor (Gleyzer et al. 2005, Cotney and Shadel 2006, Vercauteren et al. 2008).

Preceded by: [NRF1;p-PPARGC1A, NRF2 bind the TFB2M promoter](#), [NRF1, PPRC1;HCFC1:NRF2 bind the TFB2M promoter](#)

Literature references

Gleyzer, N., Scarpulla, RC., Vercauteren, K. (2005). Control of mitochondrial transcription specificity factors (TFB1M and TFB2M) by nuclear respiratory factors (NRF-1 and NRF-2) and PGC-1 family coactivators. *Mol Cell Biol*, 25, 1354-66. ↗

Gleyzer, N., Scarpulla, RC., Vercauteren, K. (2008). PGC-1-related coactivator complexes with HCF-1 and NRF-2beta in mediating NRF-2(GABP)-dependent respiratory gene expression. *J Biol Chem*, 283, 12102-11. ↗

Shadel, GS., Cotney, J. (2006). Evidence for an early gene duplication event in the evolution of the mitochondrial transcription factor B family and maintenance of rRNA methyltransferase activity in human mtTFB1 and mtTFB2. *J. Mol. Evol.*, 63, 707-17. ↗

Editions

2011-08-20	Authored, Edited	May, B.
2013-12-07	Reviewed	Lezza, AM.

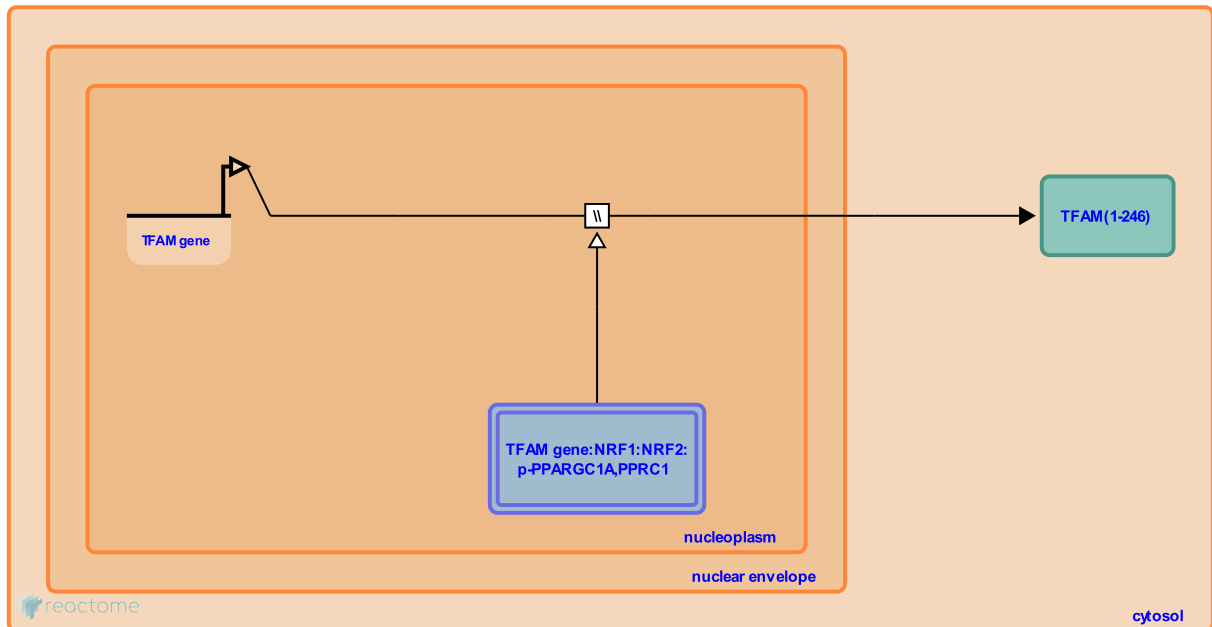
Expression of TFAM ↗

Location: [Transcriptional activation of mitochondrial biogenesis](#)

Stable identifier: R-HSA-1592246

Type: omitted

Compartments: nucleoplasm, cytosol



The TFAM gene is transcribed in the nucleus to yield mRNA and the mRNA is translated to yield precursor protein in the cytosol.

Preceded by: [NRF1:p-PPARGC1A, NRF2 bind the TFAM promoter, NRF1, PPRC1, NRF2 bind the TFAM promoter](#)

Followed by: [TFAM translocates from the cytosol to the mitochondrial matrix](#)

Literature references

- Spiegelman, BM., Cinti, S., Lowell, B., Wu, Z., Adelmant, G., Mootha, V. et al. (1999). Mechanisms controlling mitochondrial biogenesis and respiration through the thermogenic coactivator PGC-1. *Cell*, 98, 115-24. ↗
- Hayashi, J., Tominaga, K., Ohta, S., Kagawa, Y. (1993). Smaller isoform of human mitochondrial transcription factor 1: its wide distribution and production by alternative splicing. *Biochem Biophys Res Commun*, 194, 544-51. ↗
- Andersson, U., Scarpulla, RC. (2001). Pgc-1-related coactivator, a novel, serum-inducible coactivator of nuclear respiratory factor 1-dependent transcription in mammalian cells. *Mol Cell Biol*, 21, 3738-49. ↗
- Virbasius, JV., Scarpulla, RC. (1994). Activation of the human mitochondrial transcription factor A gene by nuclear respiratory factors: a potential regulatory link between nuclear and mitochondrial gene expression in organelle biogenesis. *Proc Natl Acad Sci U S A*, 91, 1309-13. ↗

Editions

2011-08-20	Authored, Edited	May, B.
2013-12-07	Reviewed	Lezza, AM.

TFAM translocates from the cytosol to the mitochondrial matrix ↗

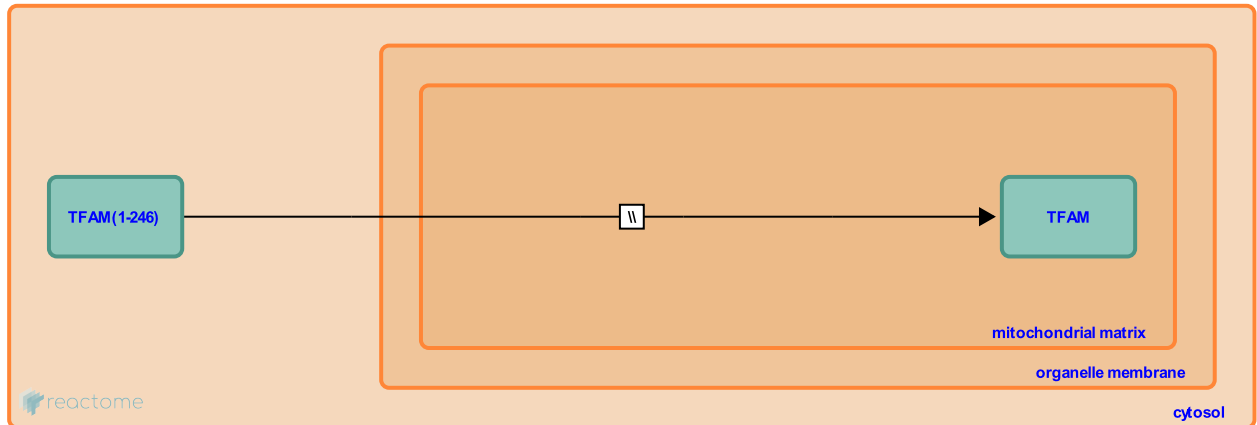
Location: [Transcriptional activation of mitochondrial biogenesis](#)

Stable identifier: R-HSA-1592229

Type: omitted

Compartments: mitochondrial matrix, cytosol

Inferred from: [Tfam translocates from the cytosol to the mitochondrial matrix \(Rattus norvegicus\)](#)



TFAM is encoded in the nucleus, synthesized as a precursor in the cytosol, and imported into the mitochondrial matrix (presumably by the SAM50 complex and the TIM23:PAM complex, reviewed in van der Laan et al. 2006). In the mitochondrial matrix TFAM binds the light strand promoter of mitochondrial DNA and regulates transcription.

Preceded by: [Expression of TFAM](#)

Literature references

Rissler, M., Rehling, P., van der Laan, M. (2006). Mitochondrial preprotein translocases as dynamic molecular machines. *FEMS Yeast Res.*, 6, 849-61. ↗

Editions

2011-08-20	Authored, Edited	May, B.
2013-12-07	Reviewed	Lezza, AM.

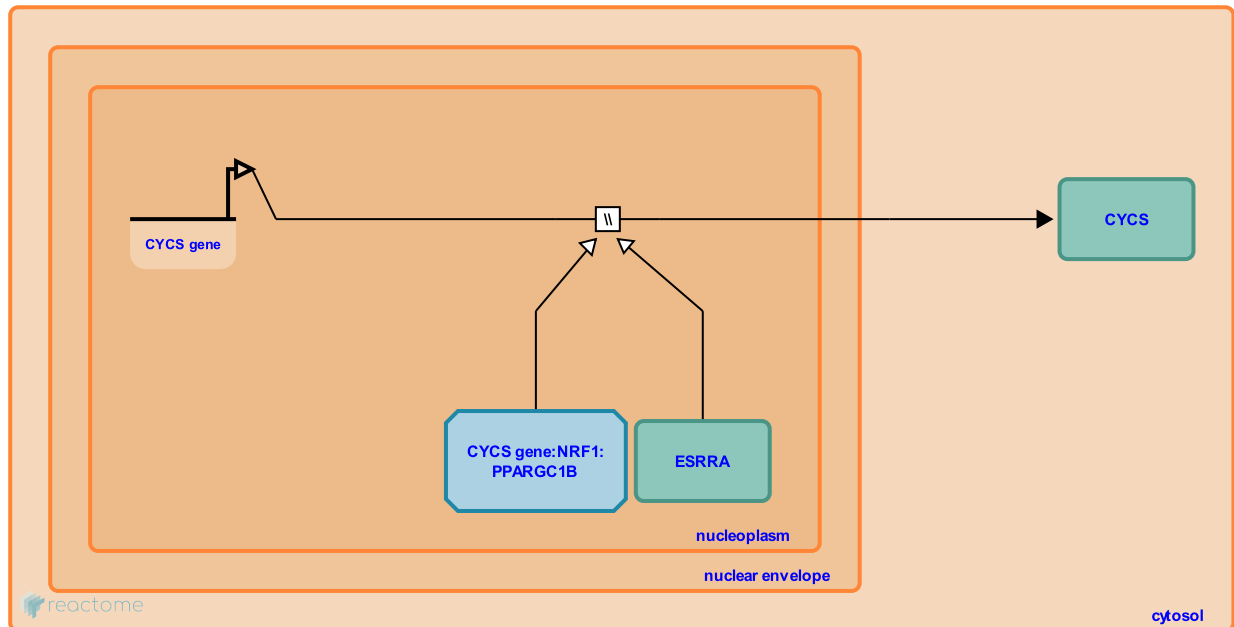
Expression of CYCS ↗

Location: [Transcriptional activation of mitochondrial biogenesis](#)

Stable identifier: R-HSA-1592231

Type: omitted

Compartments: nucleoplasm, cytosol



The gene encoding cytochrome c (CYCS) is transcribed in the nucleus to yield mRNA and the mRNA is translated in the cytosol to yield the precursor of cytochrome c, which is then imported into the mitochondrial matrix and associates with the matrix face of the inner membrane.

As inferred from rat, PGC-1beta activates expression of cytochrome c (CYCS) (Lin et al. 2003).

ERR1 (ERRalpha) probably interacts with coactivator PGC-1beta to activate expression of cytochrome c (CYCS) (Shao et al. 2010).

Preceded by: [NRF1:PPARGC1B binds the CYCS promoter](#)

Literature references

Pasko, RA., Marino, VM., Gleyzer, N., Scarpulla, RC., Vercauteren, K. (2006). PGC-1-related coactivator: immediate early expression and characterization of a CREB/NRF-1 binding domain associated with cytochrome c promoter occupancy and respiratory growth. *Mol Cell Biol*, 26, 7409-19. ↗

Editions

2011-08-20	Authored, Edited	May, B.
2013-12-07	Reviewed	Lezza, AM.

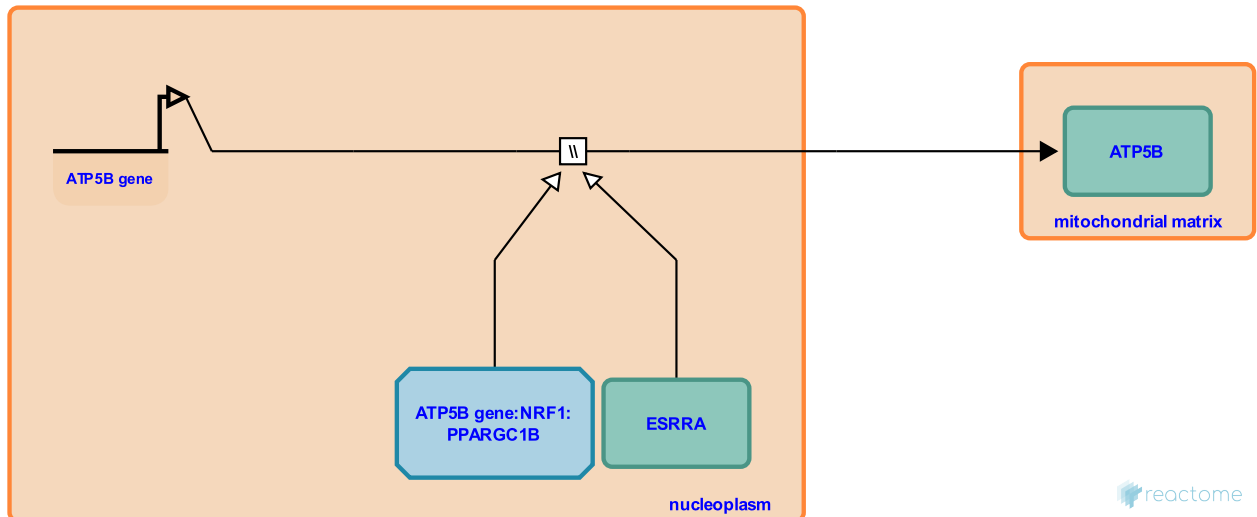
Expression of ATP5B ↗

Location: [Transcriptional activation of mitochondrial biogenesis](#)

Stable identifier: R-HSA-1592247

Type: omitted

Compartments: nucleoplasm, mitochondrial matrix



ERR1 (ERRalpha) probably interacts with PGC-1beta to activate expression of ATP5B (Shao et al. 2010).

The ATP5B (ATP synthase beta subunit) gene is transcribed in the nucleus to yield mRNA and the mRNA is translated in the cytosol to yield the ATP5B precursor, which is then imported into the mitochondrial matrix. ATP5B is a peripheral membrane protein located at the matrix face of the inner membrane within the ATP synthase complex (reviewed in Leyva et al. 2003).

Preceded by: [NRF1:PPARGC1B binds the ATP5B promoter](#)

Literature references

Leyva, JA., Bianchet, MA., Amzel, LM. (2003). Understanding ATP synthesis: structure and mechanism of the F1-ATPase (Review). *Mol. Membr. Biol.*, 20, 27-33. ↗

Izquierdo, JM. (2006). Control of the ATP synthase beta subunit expression by RNA-binding proteins TIA-1, TIAR, and HuR. *Biochem Biophys Res Commun*, 348, 703-11. ↗

Editions

2011-08-20	Authored, Edited	May, B.
2013-12-07	Reviewed	Lezza, AM.

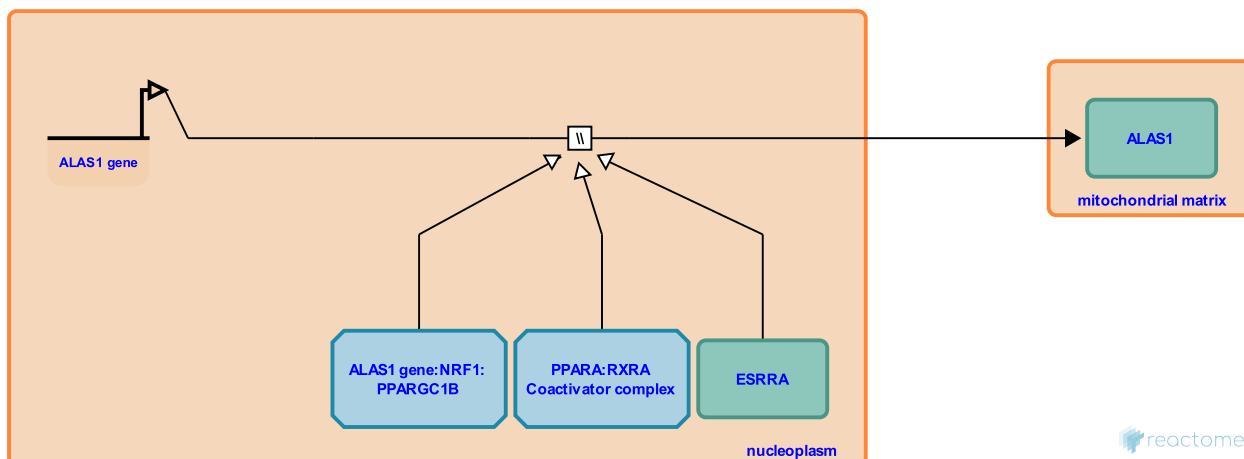
Expression of ALAS1 ↗

Location: [Transcriptional activation of mitochondrial biogenesis](#)

Stable identifier: R-HSA-1592238

Type: omitted

Compartments: nucleoplasm, mitochondrial matrix



The ALAS1 gene is transcribed to yield mRNA and the mRNA is translated in the cytosol to yield precursor protein. The ALAS1 precursor is imported into the mitochondrial matrix where it catalyzes the synthesis of 5-aminolevulinate from glycine and succinyl-CoA as part of heme biosynthesis.

ERR1 (ERRalpha) probably interacts with coactivator PG-1beta to activate ALAS1 (Shao et al. Shao et al. 2010).

Preceded by: [NRF1:PPARGC1B binds the ALAS1 promoter](#)

Literature references

Roberts, AG., Elder, GH. (2001). Alternative splicing and tissue-specific transcription of human and rodent ubiquitous 5-aminolevulinate synthase (ALAS1) genes. *Biochim Biophys Acta*, 1518, 95-105. ↗

Bonkovsky, HL., Donohue, SE., Shan, Y., Zheng, J., Lambrecht, RW. (2008). Differential regulation of human ALAS1 mRNA and protein levels by heme and cobalt protoporphyrin. *Mol Cell Biochem*, 319, 153-61. ↗

Editions

2011-08-20	Authored, Edited	May, B.
2013-12-07	Reviewed	Lezza, AM.

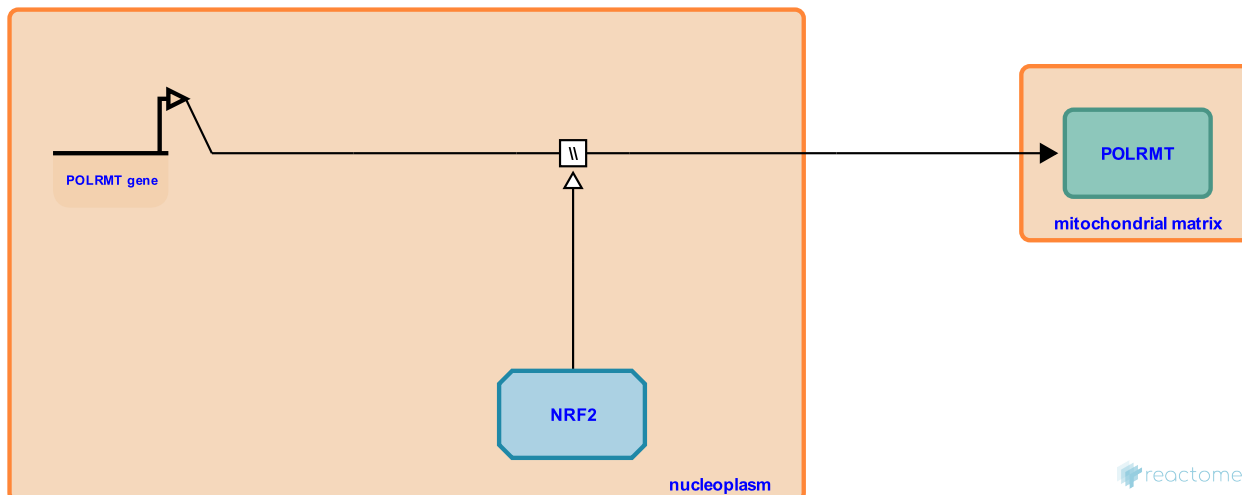
Expression of POLRMT ↗

Location: [Transcriptional activation of mitochondrial biogenesis](#)

Stable identifier: R-HSA-1592243

Type: omitted

Compartments: nucleoplasm, mitochondrial matrix



The POLRMT (mitochondrial RNA polymerase) gene is transcribed in the nucleus to yield mRNA and the mRNA is translated in the cytosol to yield POLRMT precursor, which is then imported into the mitochondria matrix. In the mitochondrial matrix POLRMT transcribes mitochondrial DNA.

Preceded by: [Formation of NRF2](#)

Literature references

Cantatore, P., Gadaleta, MN., Roberti, M., Polosa, PL., Bruni, F. (2010). Nuclear respiratory factor 2 induces the expression of many but not all human proteins acting in mitochondrial DNA transcription and replication. *J Biol Chem*, 285, 3939-48. ↗

Koonin, EV., Kravchenko, JE., Chumakov, PM., Rogozin, IB. (2005). Transcription of mammalian messenger RNAs by a nuclear RNA polymerase of mitochondrial origin. *Nature*, 436, 735-9. ↗

Editions

2011-08-20	Authored, Edited	May, B.
2013-12-07	Reviewed	Lezza, AM.

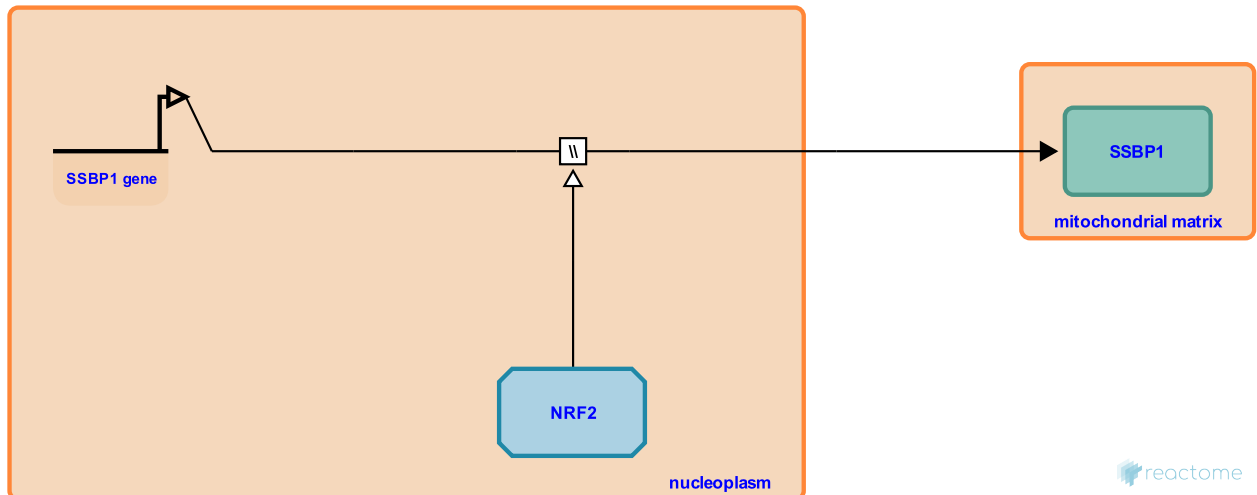
Expression of SSBP1 ↗

Location: [Transcriptional activation of mitochondrial biogenesis](#)

Stable identifier: R-HSA-1592241

Type: omitted

Compartments: nucleoplasm, mitochondrial matrix



The SSBP1 (mtSSB) gene is transcribed in the nucleus to yield mRNA and the mRNA is translated in the cytosol to yield precursor protein. The precursor SSBP1 is imported into the mitochondrial matrix where it binds single-stranded DNA.

Preceded by: [Formation of NRF2](#)

Literature references

Cantatore, P., Gadaleta, MN., Roberti, M., Polosa, PL., Bruni, F. (2010). Nuclear respiratory factor 2 induces the expression of many but not all human proteins acting in mitochondrial DNA transcription and replication. *J Biol Chem*, 285, 3939-48. ↗

Editions

2011-08-20	Authored, Edited	May, B.
2013-12-07	Reviewed	Lezza, AM.

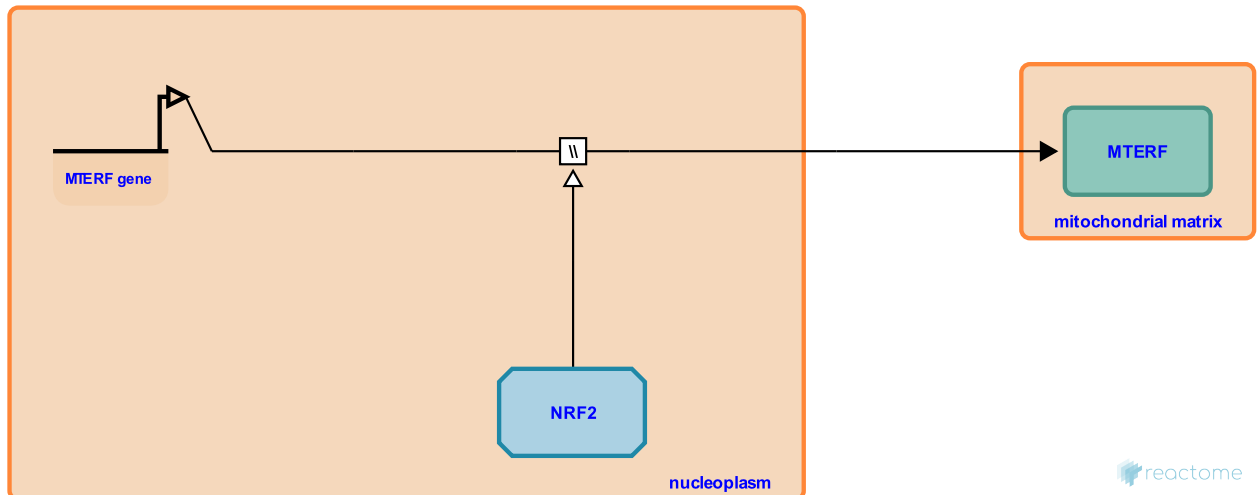
Expression of mTERF [↗](#)

Location: [Transcriptional activation of mitochondrial biogenesis](#)

Stable identifier: R-HSA-1592251

Type: omitted

Compartments: nucleoplasm, mitochondrial matrix



The mTERF gene is transcribed in the nucleus to yield mRNA and the mRNA is translated in the cytosol to yield precursor protein. mTERF is imported into the mitochondrial matrix where it plays a role in terminating transcription.

Preceded by: [Formation of NRF2](#)

Literature references

Cantatore, P., Gadaleta, MN., Roberti, M., Polosa, PL., Bruni, F. (2010). Nuclear respiratory factor 2 induces the expression of many but not all human proteins acting in mitochondrial DNA transcription and replication. *J Biol Chem*, 285, 3939-48. [↗](#)

Editions

2011-08-20	Authored, Edited	May, B.
2013-12-07	Reviewed	Lezza, AM.

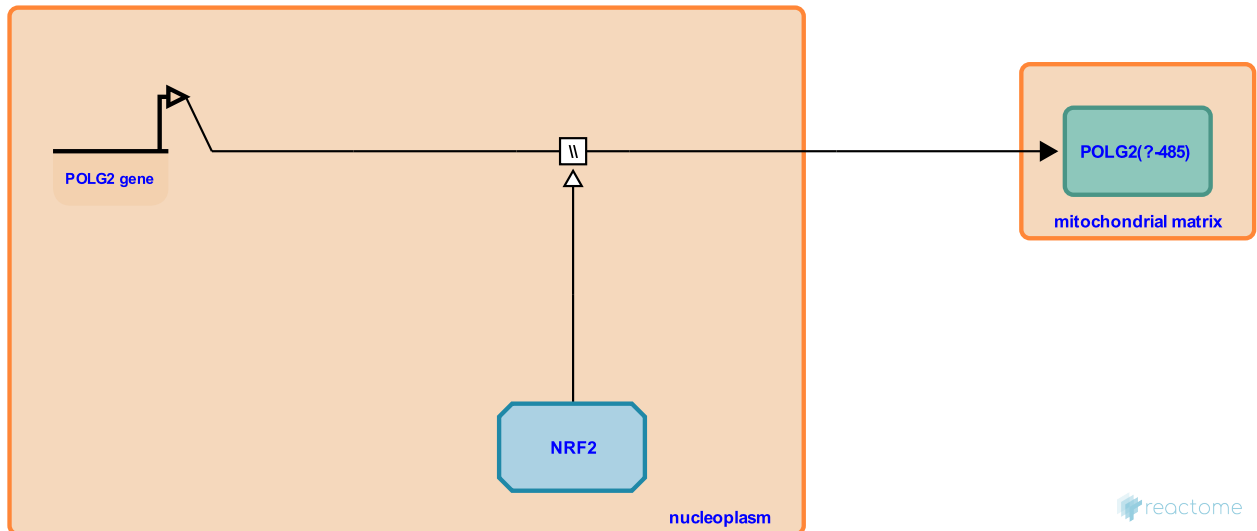
Expression of POLG2 [↗](#)

Location: [Transcriptional activation of mitochondrial biogenesis](#)

Stable identifier: R-HSA-1592235

Type: omitted

Compartments: nucleoplasm, mitochondrial matrix



The POLG2 gene is transcribed to yield mRNA and the mRNA is translated in the cytosol to yield precursor protein. POLG2 is imported into the mitochondrial matrix where it functions in DNA replication.

Preceded by: [Formation of NRF2](#)

Literature references

Cantatore, P., Gadaleta, MN., Roberti, M., Polosa, PL., Bruni, F. (2010). Nuclear respiratory factor 2 induces the expression of many but not all human proteins acting in mitochondrial DNA transcription and replication. *J Biol Chem*, 285, 3939-48. [↗](#)

Editions

2011-08-20	Authored, Edited	May, B.
2013-12-07	Reviewed	Lezza, AM.

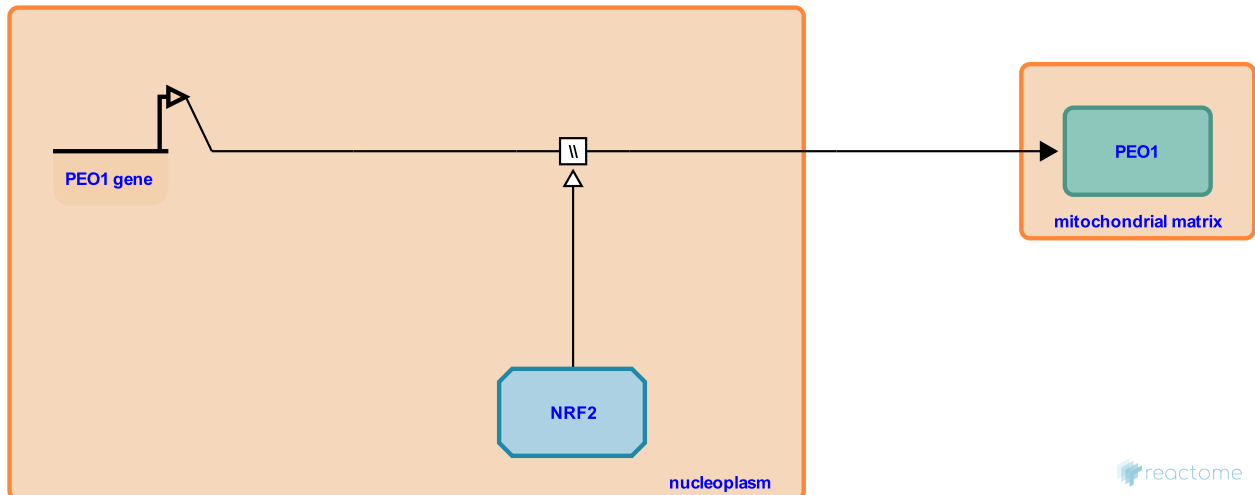
Expression of PEO1 ↗

Location: [Transcriptional activation of mitochondrial biogenesis](#)

Stable identifier: R-HSA-1592239

Type: omitted

Compartments: nucleoplasm, mitochondrial matrix



The PEO1 (TWINKLE) gene is transcribed to yield mRNA and the mRNA is translated in the cytosol to yield precursor protein. PEO1 is imported into the mitochondrial matrix where it may play a role in DNA replication.

Preceded by: [Formation of NRF2](#)

Literature references

Cantatore, P., Gadaleta, MN., Roberti, M., Polosa, PL., Bruni, F. (2010). Nuclear respiratory factor 2 induces the expression of many but not all human proteins acting in mitochondrial DNA transcription and replication. *J Biol Chem*, 285, 3939-48. ↗

Editions

2011-08-20	Authored, Edited	May, B.
2013-12-07	Reviewed	Lezza, AM.

CaMK4 phosphorylates CREB1 ↗

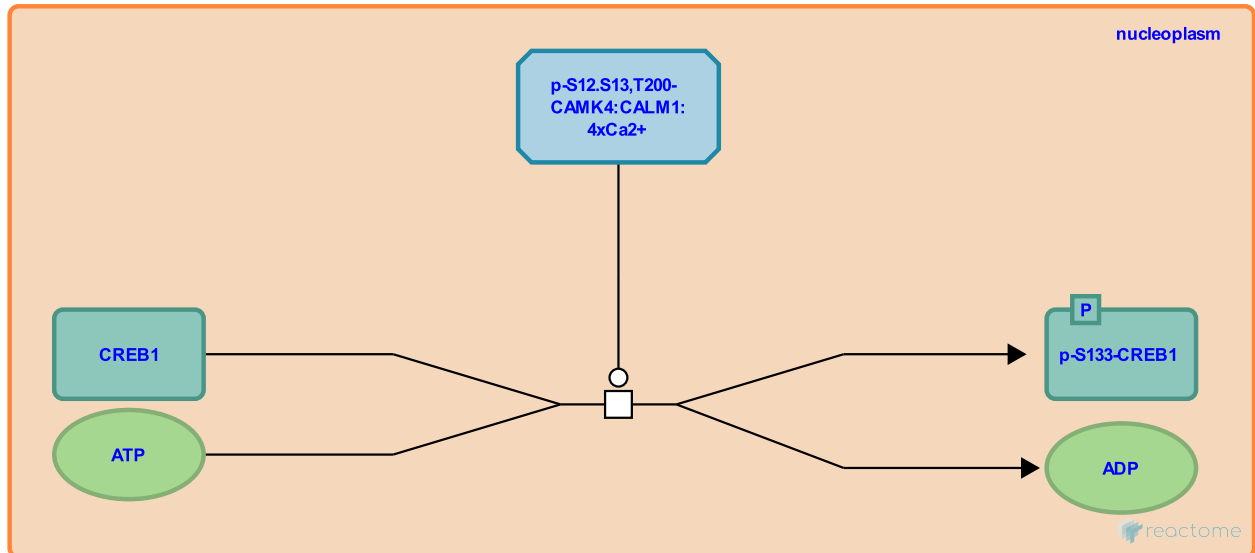
Location: [Transcriptional activation of mitochondrial biogenesis](#)

Stable identifier: R-HSA-111912

Type: transition

Compartments: nucleoplasm

Inferred from: [CaMKIV phosphorylates Creb1 \(Rattus norvegicus\)](#)



The cAMP-responsive element binding protein (CREB), a key regulator of gene expression, is activated by phosphorylation on Ser-133. Several different protein kinases possess the capability of driving this phosphorylation, making it a point of convergence for multiple intracellular signaling cascades. Work in neurons has indicated that physiologic synaptic stimulation recruits a fast calmodulin kinase IV (CaMKIV)-dependent pathway that dominates early signaling to CREB. Activated CaMKIV (CAMK4) phosphorylates CREB1 at S133, thereby initiating the transcription of CREB1-regulated set of genes, leading to protein synthesis and long lasting changes that underlie synaptic plasticity.

Followed by: [Expression of PPARGC1A \(PGC-1alpha\)](#)

Literature references

Schumann, G., Klugmann, M., Guindalini, C., de Fonseca, FR., Perreau-Lenz, S., Schütz, G. et al. (2008). Loss of the Ca²⁺/calmodulin-dependent protein kinase type IV in dopaminergic neurons enhances behavioral effects of cocaine. *Proc Natl Acad Sci U S A*, 105, 17549-54. ↗

Editions

2004-03-31	Authored	Jassal, B., Le Novere, N.
2008-11-06	Reviewed	Castagnoli, L.
2008-11-06	Edited	Jassal, B.
2009-06-02	Edited	Gillespie, ME.
2009-10-29	Authored	Mahajan, SS.
2009-11-18	Reviewed	Tukey, D.
2013-12-07	Reviewed	Lezza, AM.
2018-11-02	Reviewed	Hansen, KB., Yi, F.
2018-11-07	Edited	Orlic-Milacic, M.

Expression of PPARGC1A (PGC-1alpha) ↗

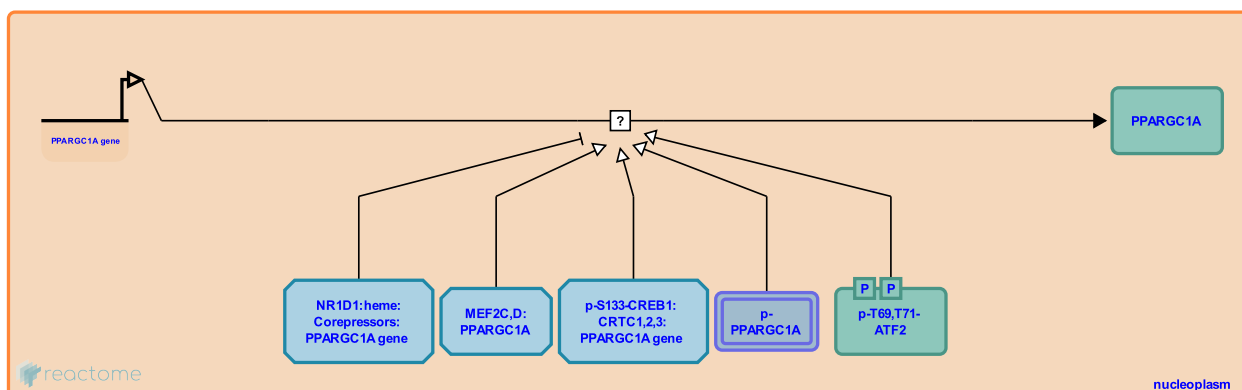
Location: [Transcriptional activation of mitochondrial biogenesis](#)

Stable identifier: R-HSA-1368140

Type: uncertain

Compartments: nucleoplasm

Inferred from: [Expression of Ppargc1a \(Pgc-1alpha\) \(Mus musculus\)](#)



The PPARGC1A gene is transcribed to yield mRNA and the mRNA is translated to yield PPARGC1A protein (Larrouy et al. 1999, Knutti et al. 2000, Pilegaard et al. 2003). PPARGC1A protein is located in the nucleus where it coactivates transcription.

As inferred from mouse homologs in liver (Herzig et al. 2001) and brown adipose tissue (Cao et al. 2004), phosphorylated CREB enhances expression of PPARGC1A (PGC-1alpha) (Handschin et al. 2003, Yoshioka et al. 2009). CRTC proteins (TORC proteins) coactivate the activation by CREB (Wu et al. 2006). CREB is phosphorylated in response to cAMP

As inferred from mouse, phosphorylated ATF2 binds the PGC-1alpha promoter and enhances expression (Cao et al. 2004, Akimoto et al. 2005, Wright et al. 2007, Akimoto et al. 2008). Intracellular calcium acting via p38 MAPK is believed to activate (phosphorylate) ATF2.

As inferred from mouse, MEF2C or MEF2D with PGC-1alpha activate expression of PGC-1alpha (Handschin et al. 2003).

NR1D1 (REV-ERBA) binds heme and the promoter of the PGC-1alpha (PPARGC1A) gene. The REV-ERBA:heme complex recruits the corepressors NCoR and HDAC3 and represses transcription.

PGC-1alpha (PPARGC1A) enhances expression of its own gene in mouse (Jager et al.2007) and in rat hepatocytes (Lin et al. 2003)

Preceded by: [CaMK4 phosphorylates CREB1](#)

Followed by: [Expression of ESRRRA \(ERR1, ERRalpha\)](#), [Expression of PERM1](#), [Expression of SIRT3](#)

Literature references

Saltin, B., Pilegaard, H., Neufer, PD. (2003). Exercise induces transient transcriptional activation of the PGC-1alpha gene in human skeletal muscle. *J Physiol*, 546, 851-8. ↗

Kralli, A., Kaul, A., Knutti, D. (2000). A tissue-specific coactivator of steroid receptors, identified in a functional genetic screen. *Mol Cell Biol*, 20, 2411-22. ↗

Andreelli, F., Langin, D., Laville, M., Vidal, H., Larrouy, D. (1999). Cloning and mRNA tissue distribution of human PPARGgamma coactivator-1. *Int J Obes Relat Metab Disord*, 23, 1327-32. ↗

Editions

2011-06-22	Authored, Edited	May, B.
2013-12-07	Reviewed	Lezza, AM.
2021-01-23	Reviewed	Somers, J.

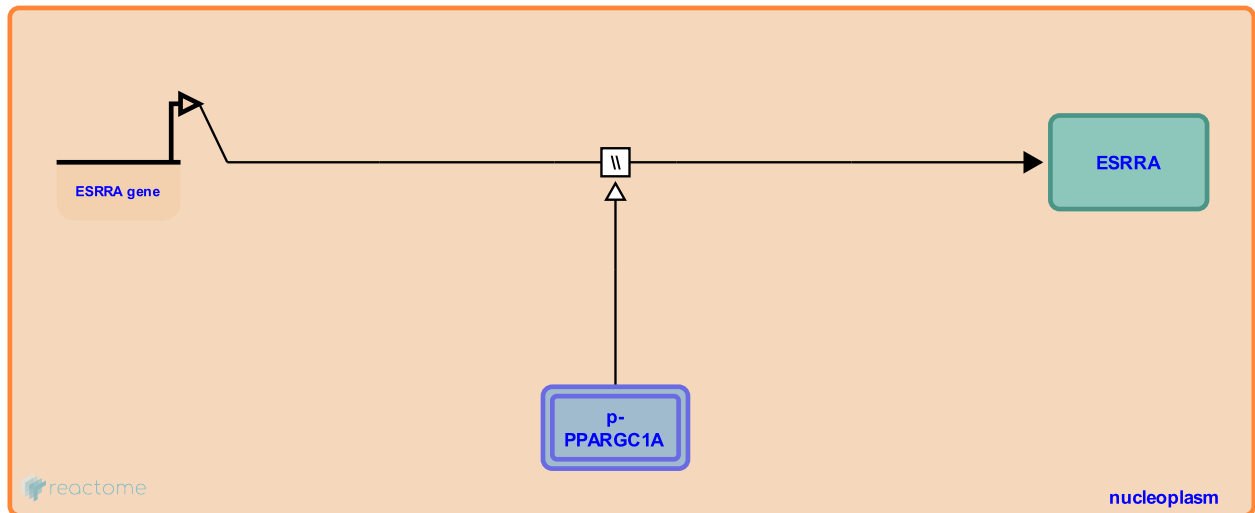
Expression of ESRRA (ERR1, ERRalpha) ↗

Location: [Transcriptional activation of mitochondrial biogenesis](#)

Stable identifier: R-HSA-1605428

Type: omitted

Compartments: nucleoplasm



The ERR1 (ERRalpha) gene is transcribed to yield mRNA and the mRNA is translated to yield protein. ERR1 is a nuclear receptor that interacts with PPARGC1A (PGC-1alpha) and regulates energy metabolism.

Preceded by: [Expression of PPARGC1A \(PGC-1alpha\)](#)

Literature references

Teng, CT., Shi, H., Fu, K., Shigeta, H., O'Brian, G., Yang, N. (1997). Human estrogen receptor-like 1 (ESRL1) gene: genomic organization, chromosomal localization, and promoter characterization. *Genomics*, 44, 52-60. ↗

Laudet, V., Aubin, JE., Dittmar, T., Vanacker, JM., Fournier, B., Desbiens, X. et al. (1997). The ERR-1 orphan receptor is a transcriptional activator expressed during bone development. *Mol Endocrinol*, 11, 905-16. ↗

Editions

2011-09-10	Authored, Edited	May, B.
2013-12-07	Reviewed	Lezza, AM.

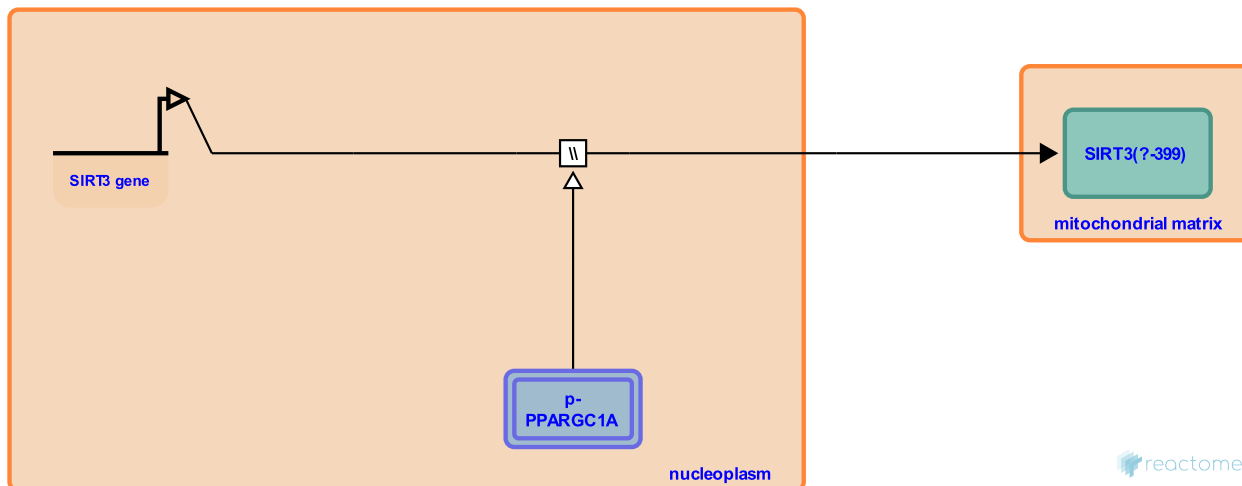
Expression of SIRT3 ↗

Location: [Transcriptional activation of mitochondrial biogenesis](#)

Stable identifier: R-HSA-1605535

Type: omitted

Compartments: nucleoplasm, mitochondrial matrix



As inferred from mouse, PGC-1alpha (PPARGC1A) activates expression of SIRT3 (Kong et al. 2010). The SIRT3 gene is transcribed to yield mRNA and the mRNA is translated in the cytosol to yield precursor protein. SIRT3 is imported into the mitochondrial matrix where it deacetylates, and hence activates, target proteins

Preceded by: [Expression of PPARGC1A \(PGC-1alpha\)](#)

Literature references

- Cooper, HM., Spelbrink, JN. (2008). The human SIRT3 protein deacetylase is exclusively mitochondrial. *Biochem J*, 411, 279-85. ↗
- Barrett, JC., Michishita, E., Horikawa, I., Burneskis, JM., Park, JY. (2005). Evolutionarily conserved and nonconserved cellular localizations and functions of human SIRT proteins. *Mol Biol Cell*, 16, 4623-35. ↗
- Reinberg, D., Scher, MB., Vaquero, A. (2007). SirT3 is a nuclear NAD⁺-dependent histone deacetylase that translocates to the mitochondria upon cellular stress. *Genes Dev*, 21, 920-8. ↗
- Feinberg, AP., Onyango, P., McCaffery, JM., Boeke, JD., Celic, I. (2002). SIRT3, a human SIR2 homologue, is an NAD-dependent deacetylase localized to mitochondria. *Proc Natl Acad Sci U S A*, 99, 13653-8. ↗

Editions

2011-09-10	Authored, Edited	May, B.
2013-12-07	Reviewed	Lezza, AM.

Expression of PERM1 ↗

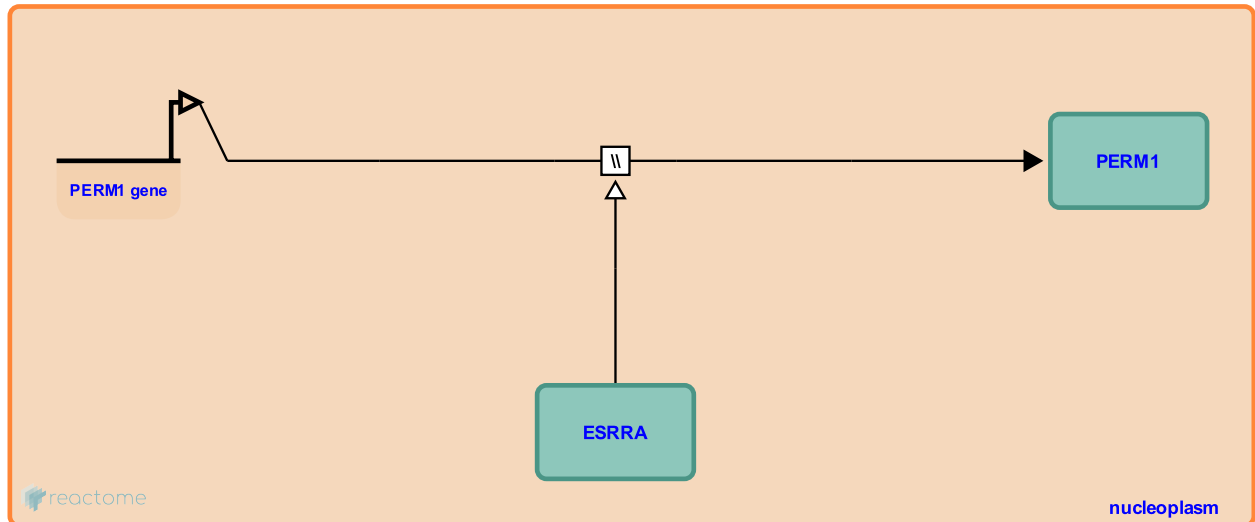
Location: [Transcriptional activation of mitochondrial biogenesis](#)

Stable identifier: R-HSA-8940309

Type: omitted

Compartments: nucleoplasm

Inferred from: [Expression of Perm1 \(Mus musculus\)](#)



As inferred from the mouse homolog, the PERM1 gene is transcribed to yield mRNA, the mRNA is translated to yield protein. The PERM1 gene is expressed selectively in muscle where it is activated by PPARGC1A via the estrogen receptor ESRRRA, which binds regulatory regions of the PERM1 gene. In mouse, Perm1 expression in adult skeletal muscle promotes mitochondrial biogenesis, oxidative capacity and vascularization, without affecting fiber type switching. In mouse, expression of Perm1 is activated by exercise.

Preceded by: [Expression of PPARGC1A \(PGC-1alpha\)](#)

Editions

2016-09-25	Authored, Edited	May, B.
2016-11-20	Reviewed	Kralli, A.

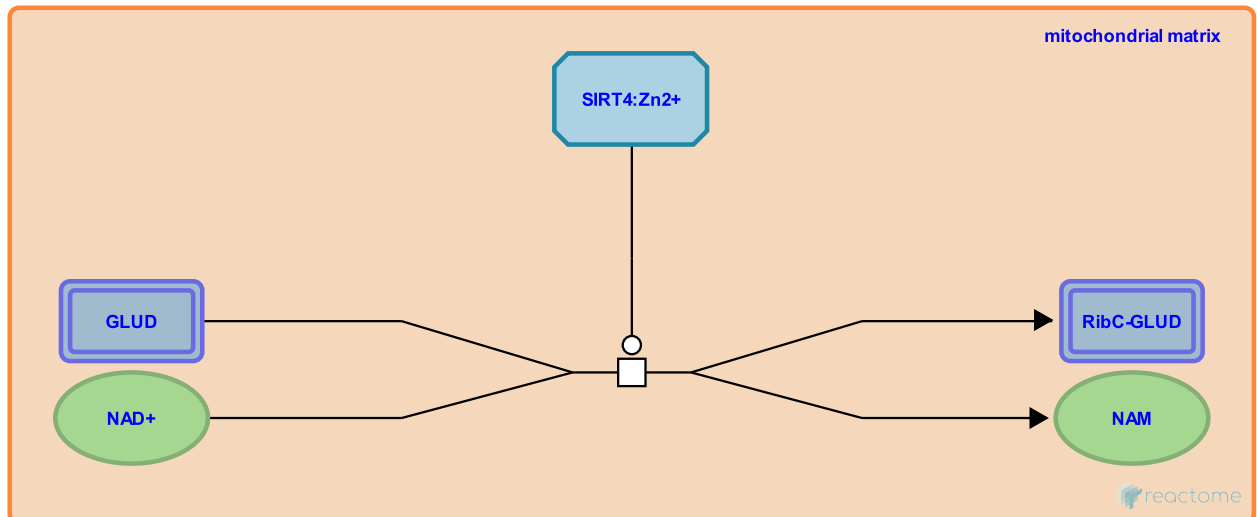
SIRT4 transfers ADPRib to GLUD ↗

Location: [Transcriptional activation of mitochondrial biogenesis](#)

Stable identifier: R-HSA-5688276

Type: transition

Compartments: mitochondrial matrix



Sirtuin 4 (SIRT4) is a mitochondrial ADP-ribosyltransferase and deacetylase. It uses NAD⁺ to ADP-ribosylate glutamate dehydrogenase (GLUD), reducing its enzyme activity by at least 50%, leading to reduced insulin secretion in pancreatic beta cells (Haigis et al. 2006, Ahuja et al. 2007).

Literature references

Waltregny, D., North, B.J., Maechler, P., Verdin, E., Carobbio, S., Schwer, B. et al. (2007). Regulation of insulin secretion by SIRT4, a mitochondrial ADP-ribosyltransferase. *J. Biol. Chem.*, 282, 33583-92. ↗

Editions

2015-04-15	Authored	Jupe, S.
2017-02-01	Reviewed	Haigis, M.
2017-02-01	Edited	Jupe, S.

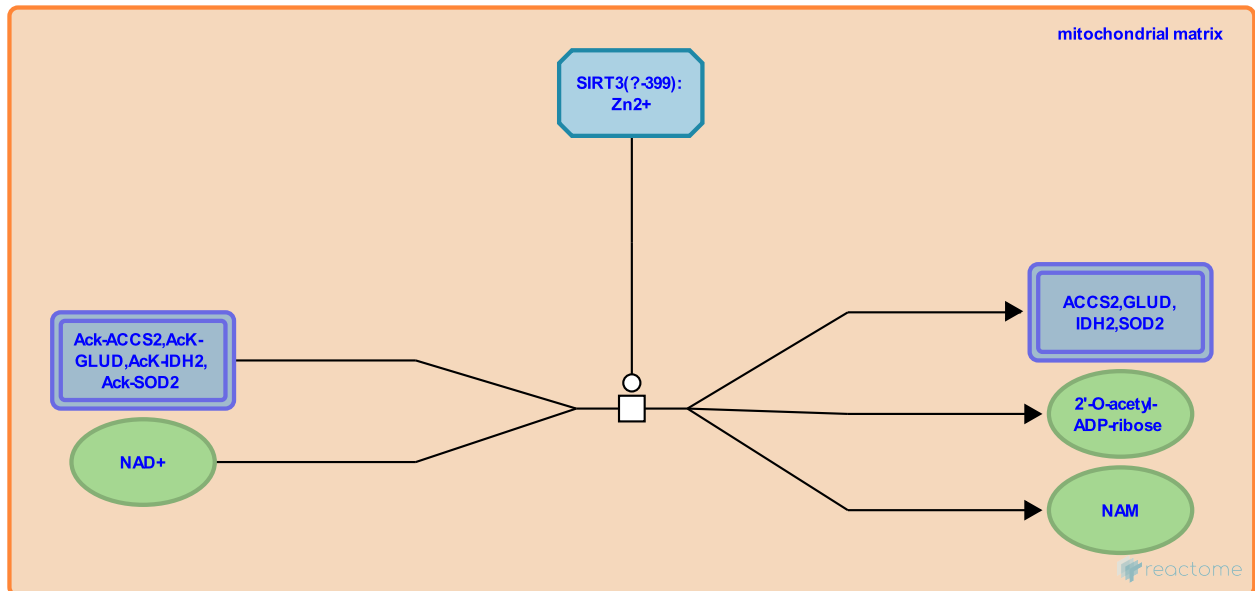
SIRT3 deacetylates ACCS2, GLUD, IDH2, SOD2 ↗

Location: [Transcriptional activation of mitochondrial biogenesis](#)

Stable identifier: R-HSA-5688289

Type: transition

Compartments: mitochondrial matrix



Sirtuin 3 (SIRT3) is the most extensively studied of the mitochondrial sirtuins. It deacetylates and thereby activates Acetyl-CoA synthetase 2 (ACCS2), Glutamate dehydrogenase (GLUD), Isocitrate dehydrogenase 2 (IDH2) and Superoxide dismutase 2 (SOD2) (Schwer et al. 2006, Lombard et al. 2007, Schlicker et al. 2008, Tao et al. 2010).

Literature references

Murphy, A., Guarente, LP., Kim, J., Alt, FW., Verdin, E., Haigis, M. et al. (2007). Mammalian Sir2 homolog SIRT3 regulates global mitochondrial lysine acetylation. *Mol. Cell. Biol.*, 27, 8807-14. ↗

Schwer, B., Verdin, RO., Andersen, JS., Verdin, E., Bunkenborg, J. (2006). Reversible lysine acetylation controls the activity of the mitochondrial enzyme acetyl-CoA synthetase 2. *Proc Natl Acad Sci U S A*, 103, 10224-9. ↗

Papatheodorou, P., Schlicker, C., Becker, CF., Steegborn, C., Gertz, M., Kachholz, B. (2008). Substrates and regulation mechanisms for the human mitochondrial sirtuins Sirt3 and Sirt5. *J. Mol. Biol.*, 382, 790-801. ↗

Editions

2015-04-15	Authored	Jupe, S.
2017-02-01	Reviewed	Haigis, M.
2017-02-01	Edited	Jupe, S.

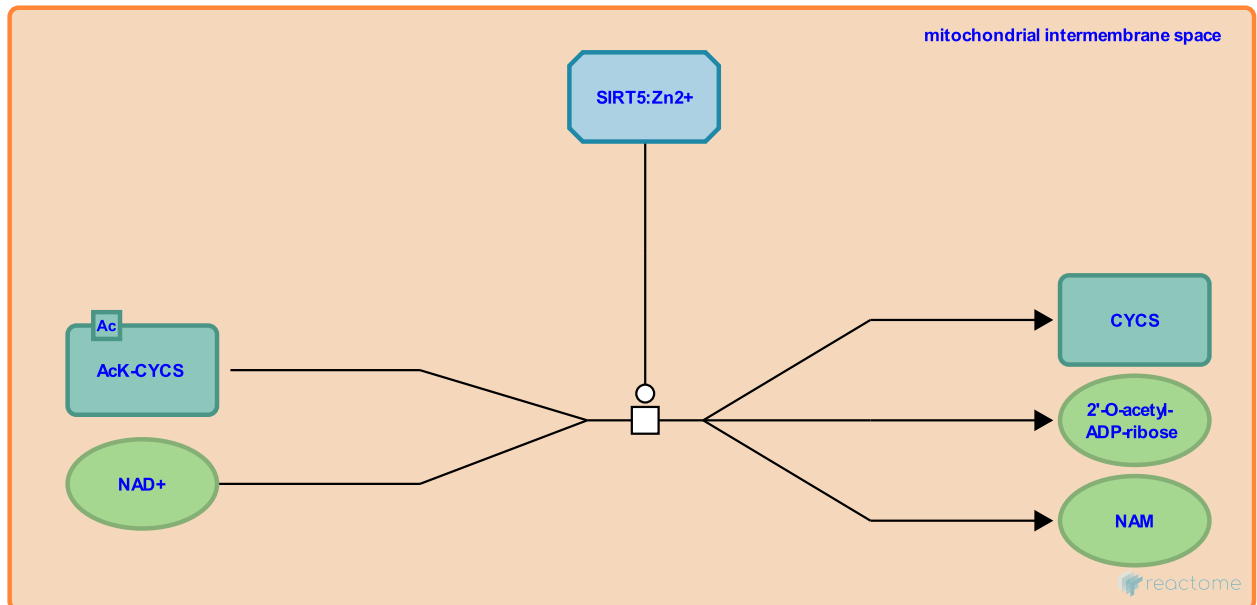
SIRT5 deacetylates Cytochrome C ↗

Location: [Transcriptional activation of mitochondrial biogenesis](#)

Stable identifier: R-HSA-5688294

Type: transition

Compartments: mitochondrial intermembrane space



Sirtuin 5 has been shown to deacetylate Cytochrome C in the the mitochondrial intermembrane space (Schlicker et al. 2008). The functional significance of this is unknown (Bao & Sack 2010).

Literature references

Papatheodorou, P., Schlicker, C., Becker, CF., Steegborn, C., Gertz, M., Kachholz, B. (2008). Substrates and regulation mechanisms for the human mitochondrial sirtuins Sirt3 and Sirt5. *J. Mol. Biol.*, 382, 790-801. ↗

Editions

2015-04-15	Authored	Jupe, S.
2017-02-01	Reviewed	Haigis, M.
2017-02-01	Edited	Jupe, S.

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