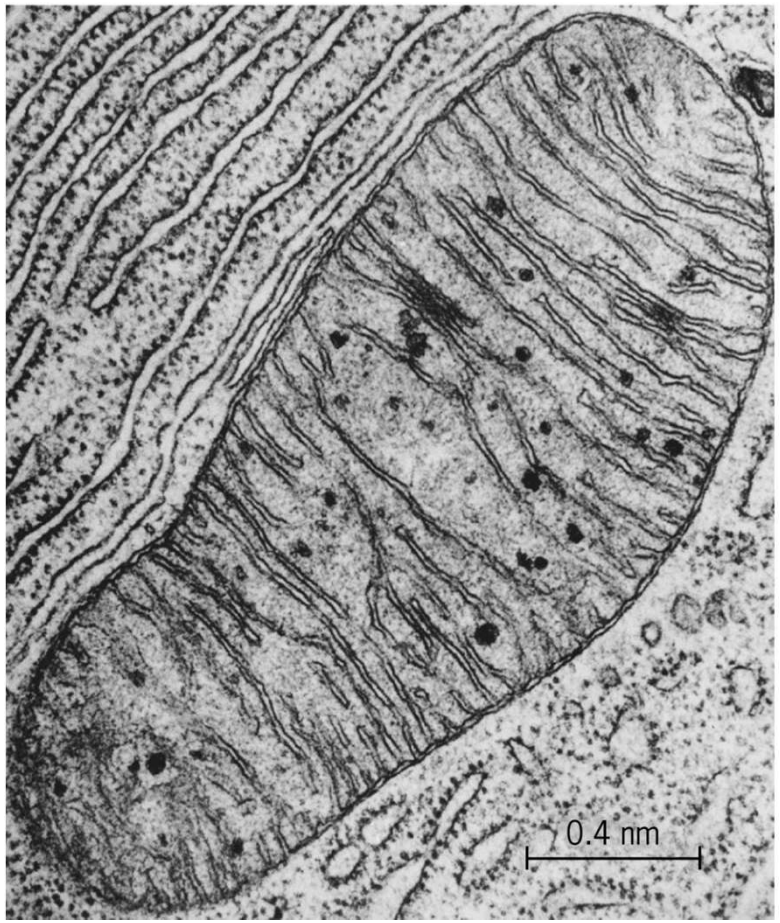
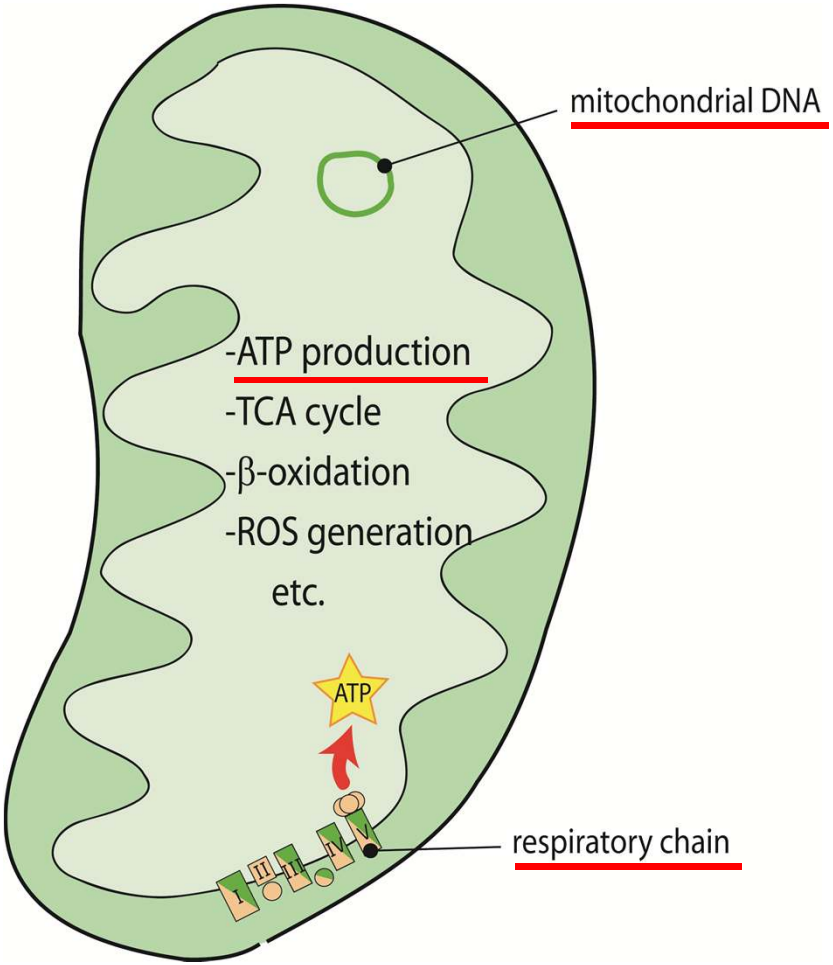
Mitochondrial biogenesis and diabetes, functional of confirmation mtDNA transcription factors

Chan Bae Park
Ajou Univ. School of Medicine

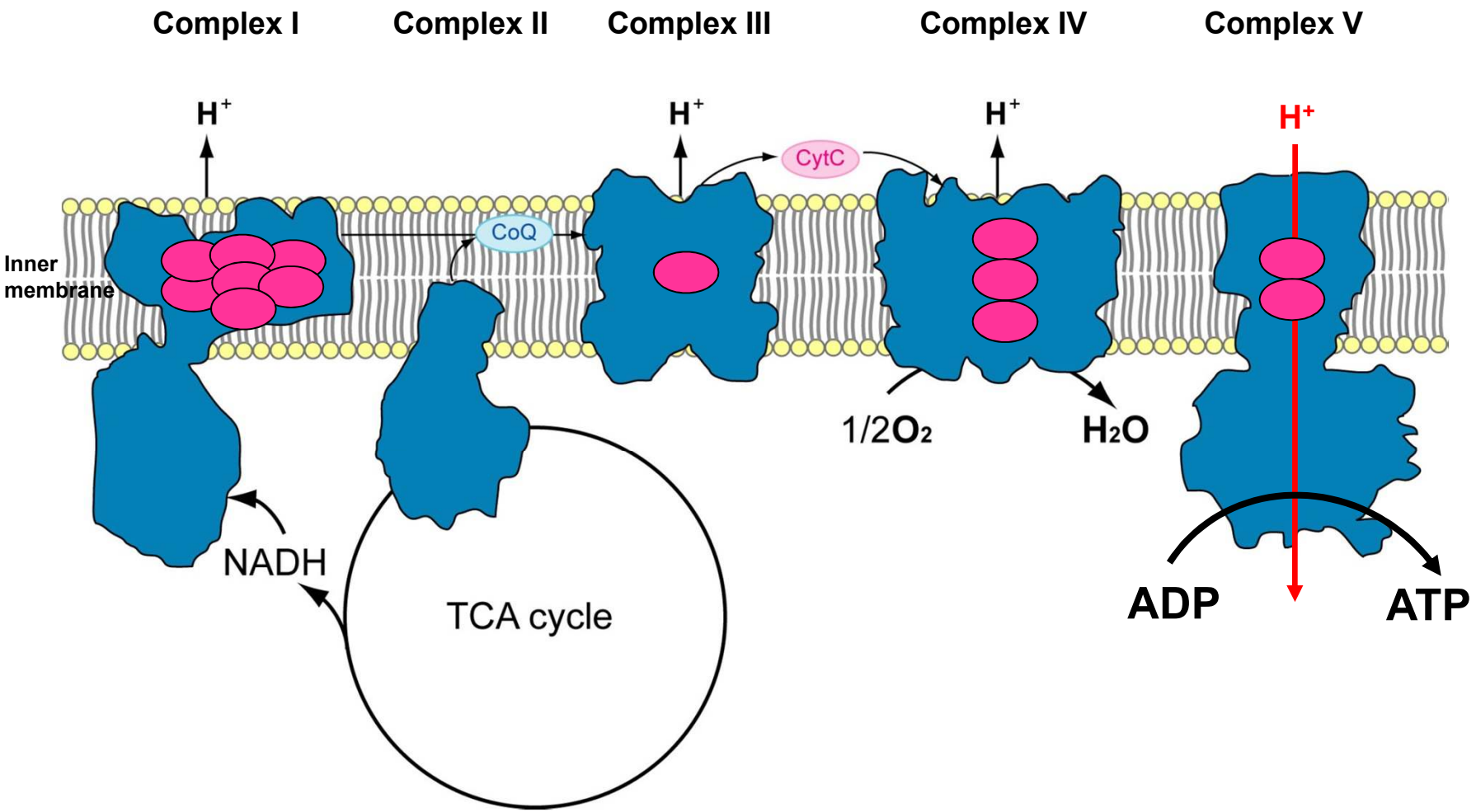
Mitochondria perform diverse functions



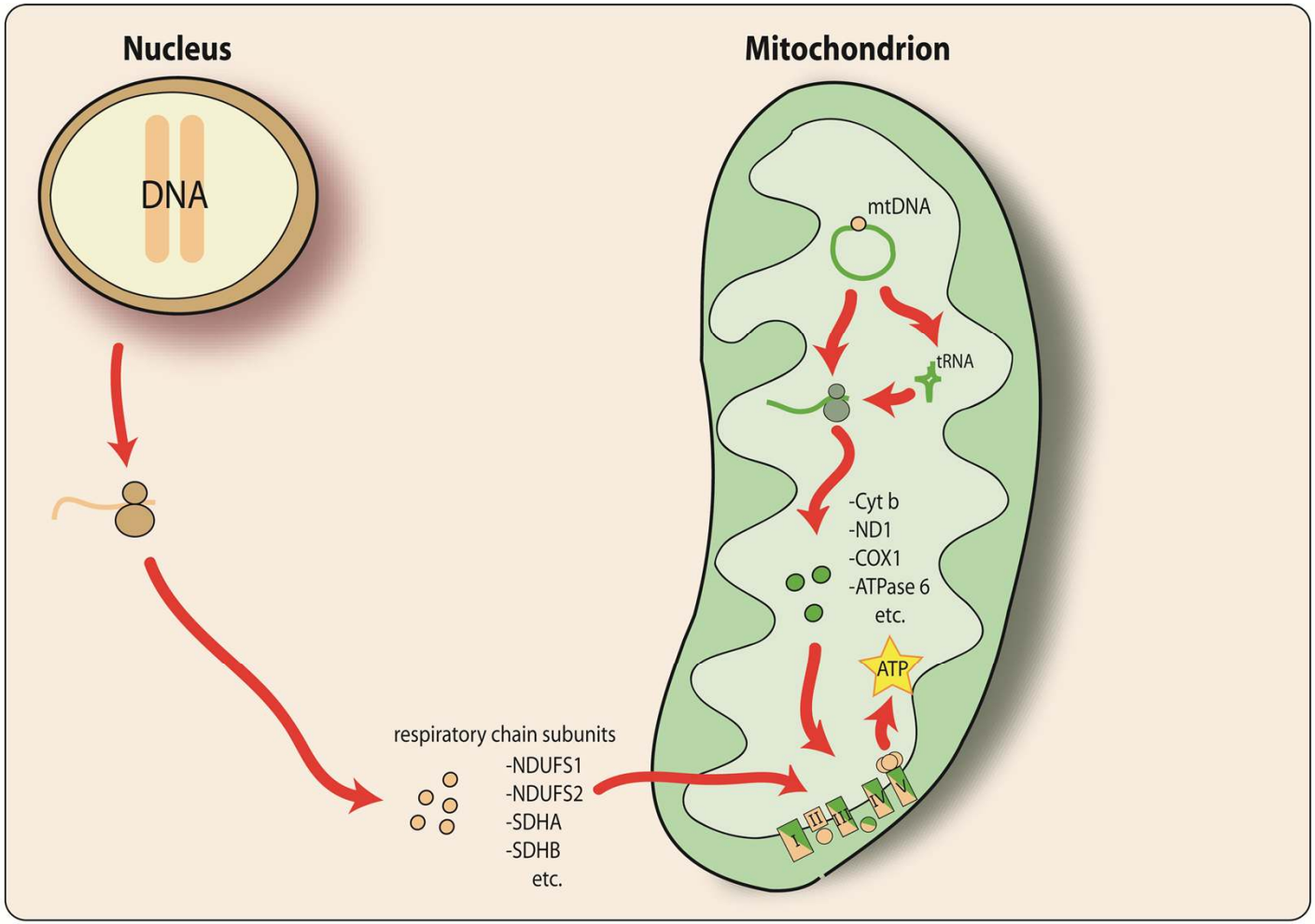
(Courtesy of K. R. Porter, University of Maryland Baltimore County)



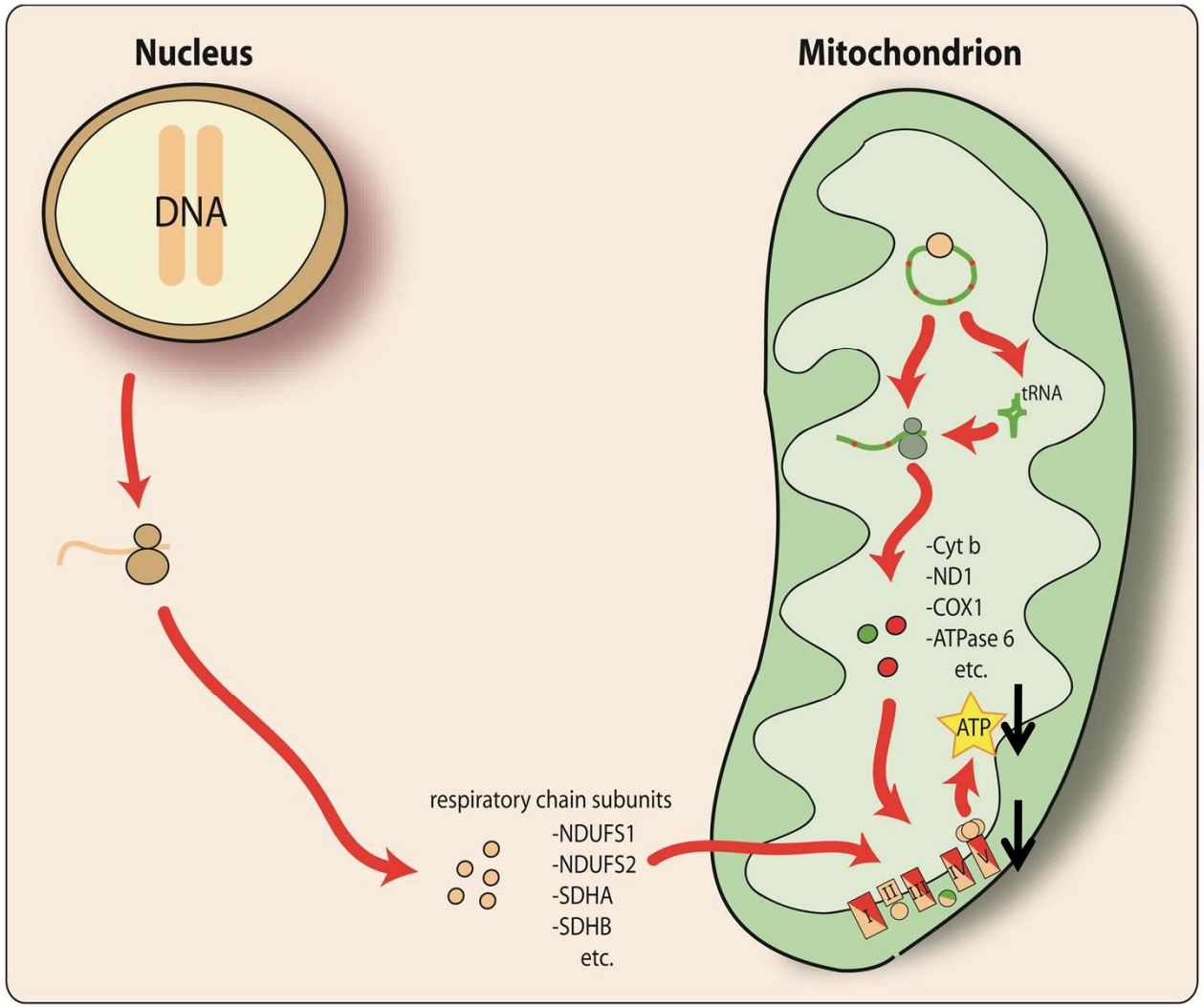
Respiratory chain subunits are encoded in two genomes



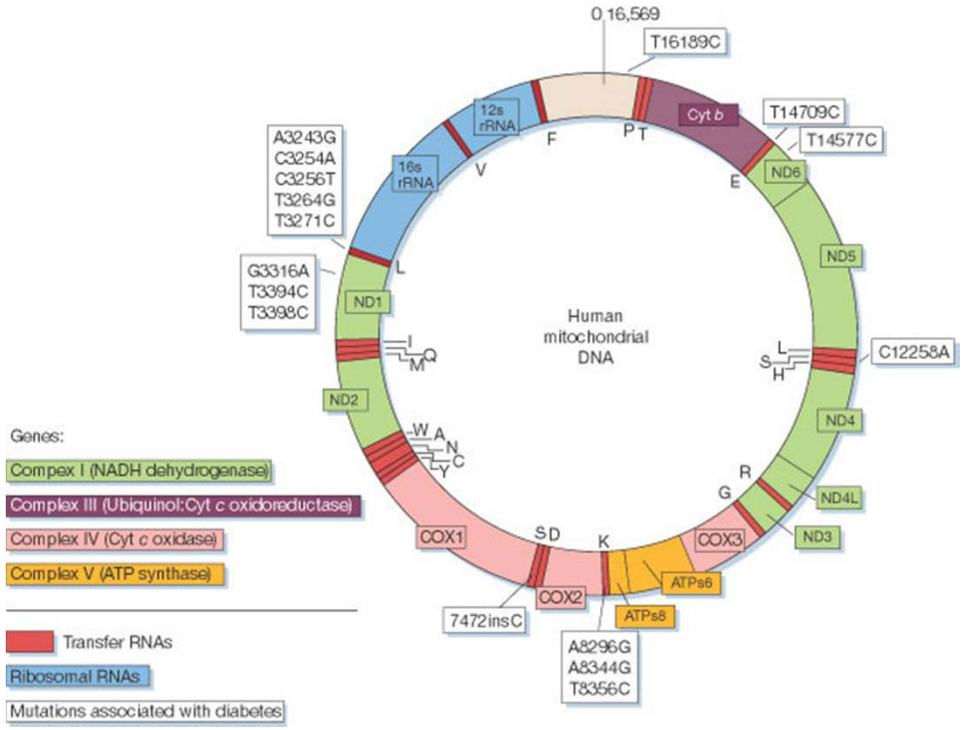
Respiratory chain subunits are encoded in two genomes



MtDNA mutation cause mitochondrial dysfunction



Human mtDNA mutations associated with diabetes



Maechler and Wolleim; Nature(2001)

Human mtDNA mutations associated with diabetes

Diabetologia (2008) 51:602–608
DOI 10.1007/s00125-008-0933-z

ARTICLE

A mitochondrial DNA variant at position 16189 is associated with type 2 diabetes mellitus in Asians

K. S. Park · J. C. Chan · L.-M. Chuang · S. Suzuki · E. Araki · K. Nanjo · L. Ji · M. Ng · M. Nishi · H. Furuta · T. Shirotani · B. Y. Ahn · S. S. Chung · H.-K. Min · S. W. Lee · J. H. Kim · Y. M. Cho · H. K. Lee · for The Study Group of Molecular Diabetology in Asia

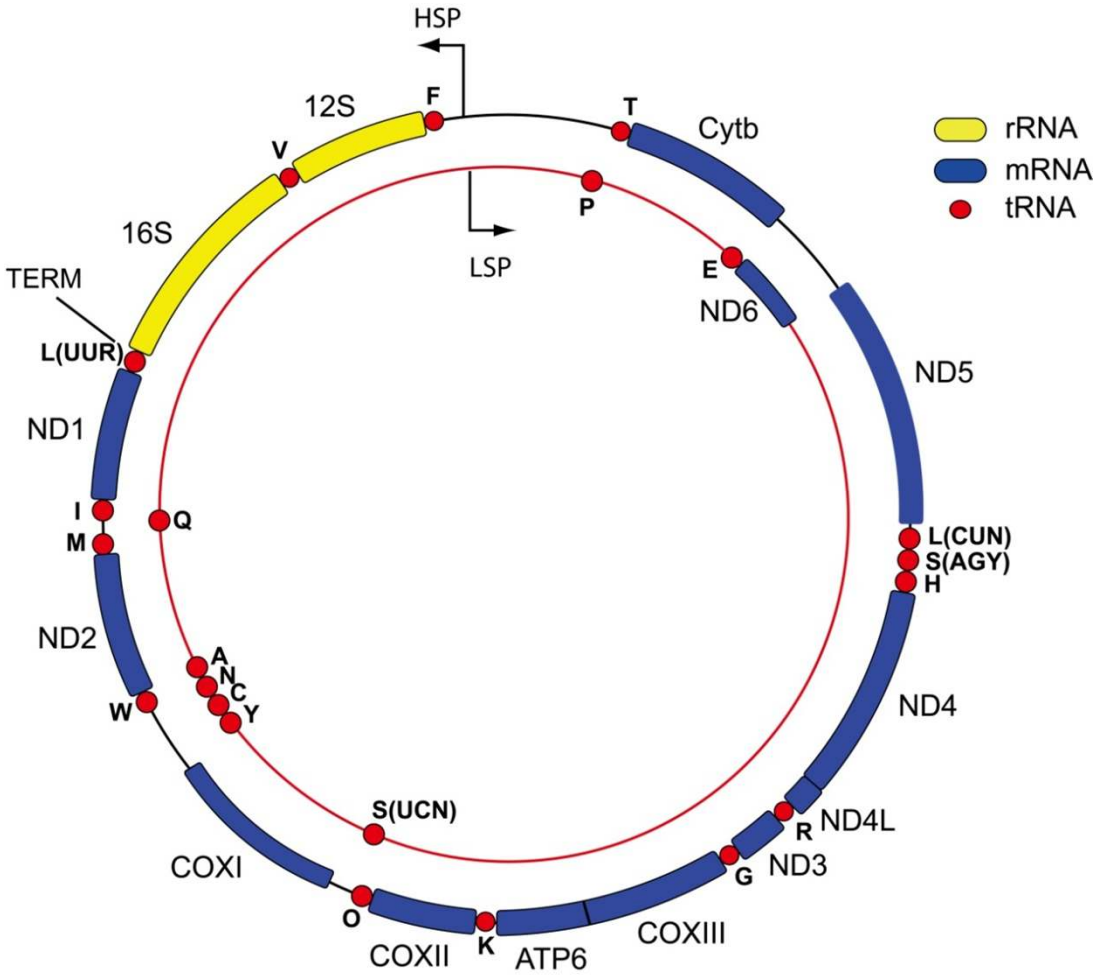
Received: 7 November 2007 / Accepted: 1 January 2008 / Published online: 5 February 2008

Park et al; Diabetalogia (2008)

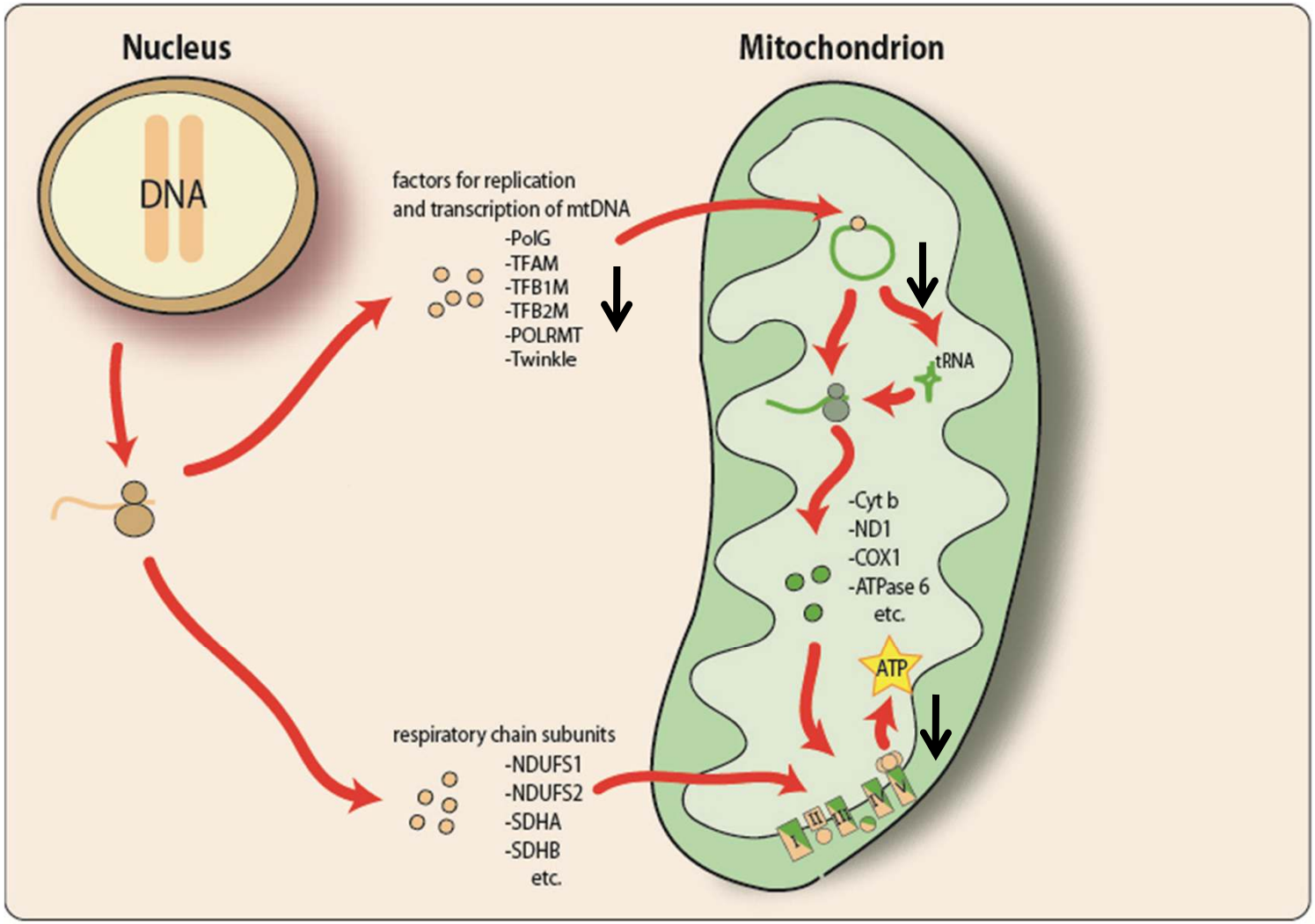
Mammalian mitochondrial DNA (mtDNA)

HSP
2 rRNA
12 mRNA
14 tRNA

LSP
1 mRNA
8 tRNA
Replication primer



MtDNA expression require nuclear factors



Human mtDNA expression factor TFB1M is associated with diabetes

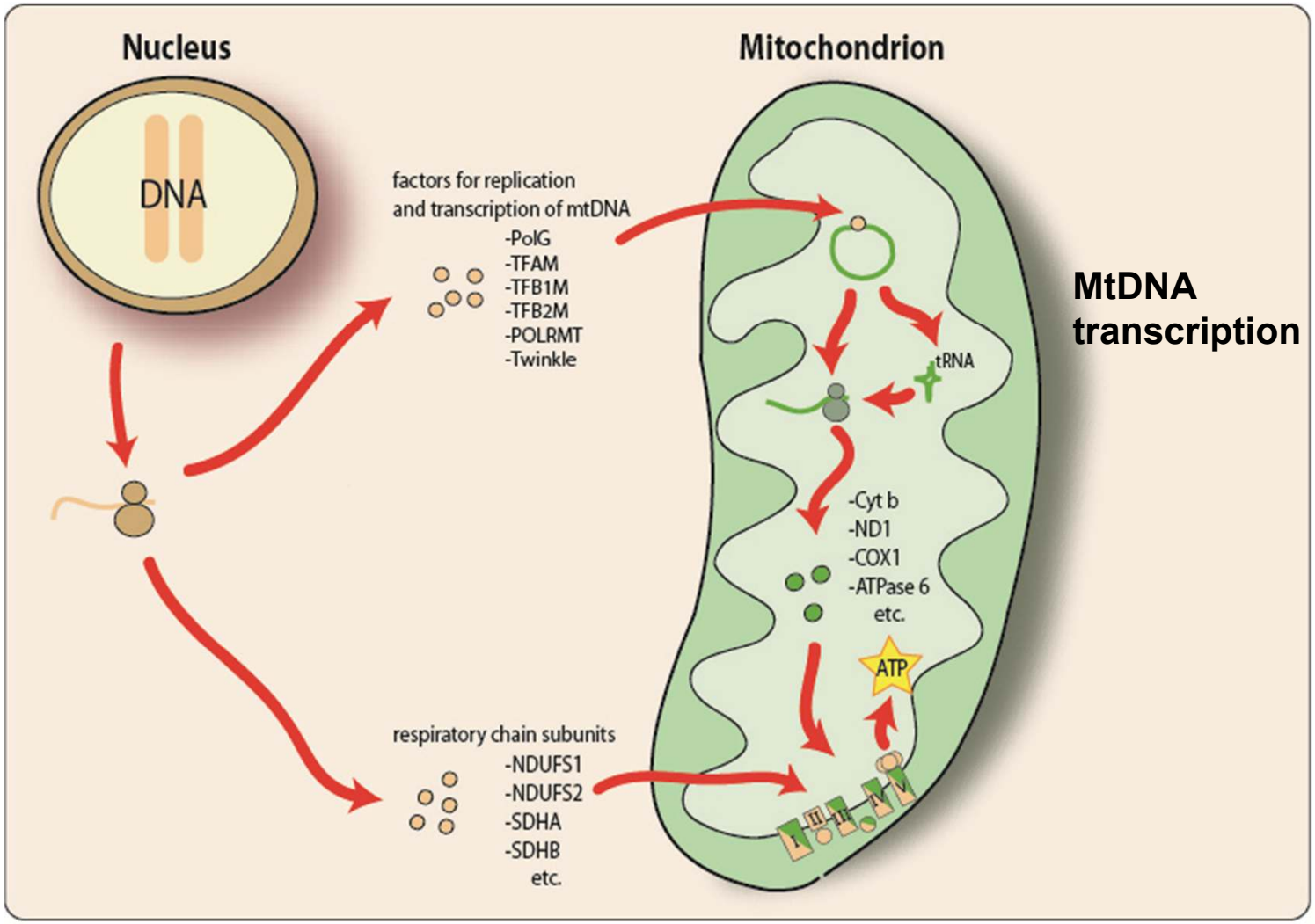
Cell Metabolism
Article

A Common Variant in *TFB1M* Is Associated with Reduced Insulin Secretion and Increased Future Risk of Type 2 Diabetes

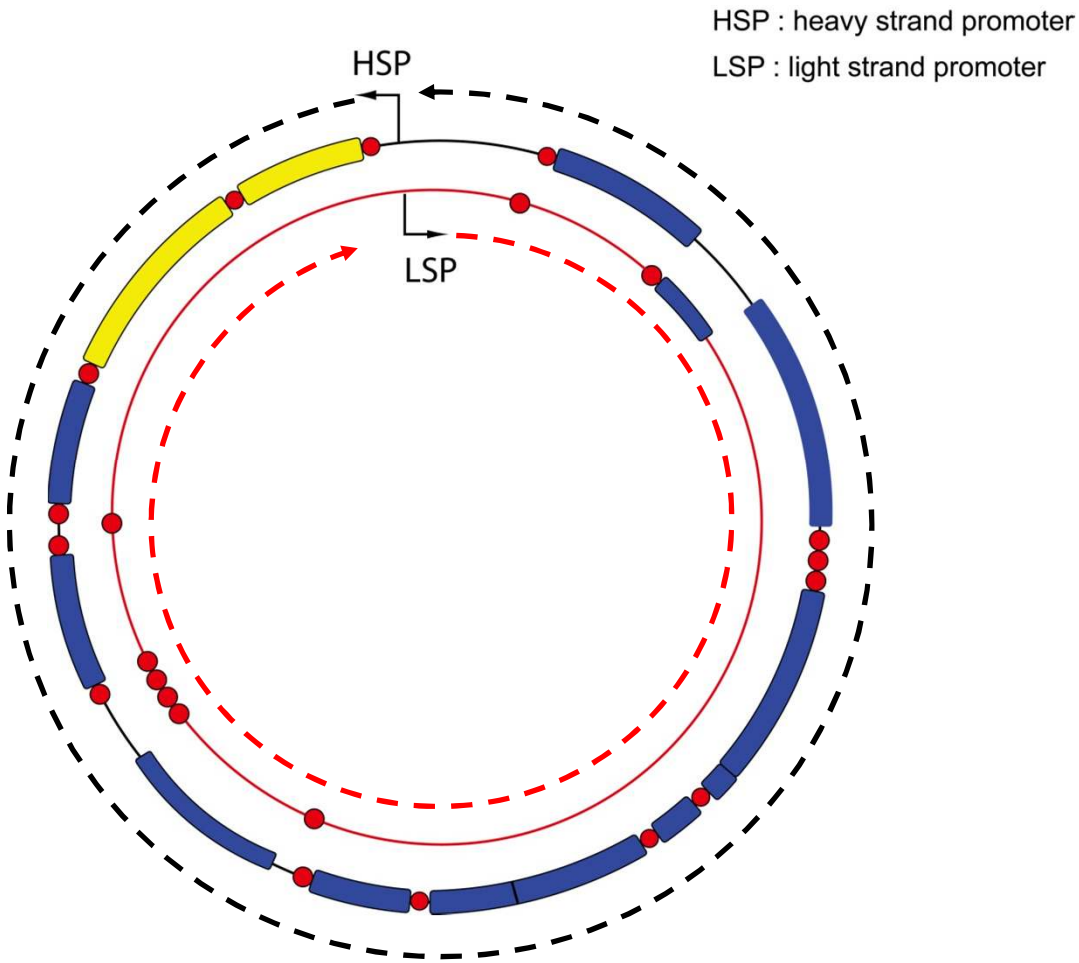
Thomas Koeck,[1] Anders H. Olsson,[1] Marloes Dekker Nitert,[1] Vladimir V. Sharoyko,[1] Claes Ladenvall,[1] Olga Kotova,[1] Erwin Reiling,[2] Tina Rönn,[1] Hemang Parikh,[1] Jalal Taneera,[1] Johan G. Eriksson,[3,4] Metodi D. Metodiev,[5] Nils-Göran Larsson,[5] Alexander Balhuizen,[1] Holger Luthman,[1] Alena Stančáková,[6] Johanna Kuusisto,[6] Markku Laakso,[6] Pernille Poulsen,[7,8] Allan Vaag,[7] Leif Groop,[1] Valeriya Lyssenko,[1] Hindrik Mulder,[1,9] and Charlotte Ling[1,9,*]
[1]Department of Clinical Sciences, Lund University Diabetes Centre, CRC, Scania University Hospital, 205 02 Malmö, Sweden
[2]Department of Molecular Cell Biology, Leiden University Medical Center, Leiden, The Netherlands
[3]National Institute for Health and Welfare, Helsinki, Finland
[4]Department of General Practice and Primary Health Care, University of Helsinki, Helsinki, Finland
[5]Max Planck Institute for Biology of Ageing, Cologne D-50931, Germany
[6]Department of Medicine, University of Eastern Finland, 70210 Kuopio, Finland
[7]Steno Diabetes Center, 2820 Gentofte, Denmark
[8]Novo Nordisk, DK-2860 Soeborg, Denmark
[9]These authors contributed equally to this work
*Correspondence: charlotte.ling@med.lu.se
DOI 10.1016/j.cmet.2010.12.007

Koeck et al; Cell Metab (2010)

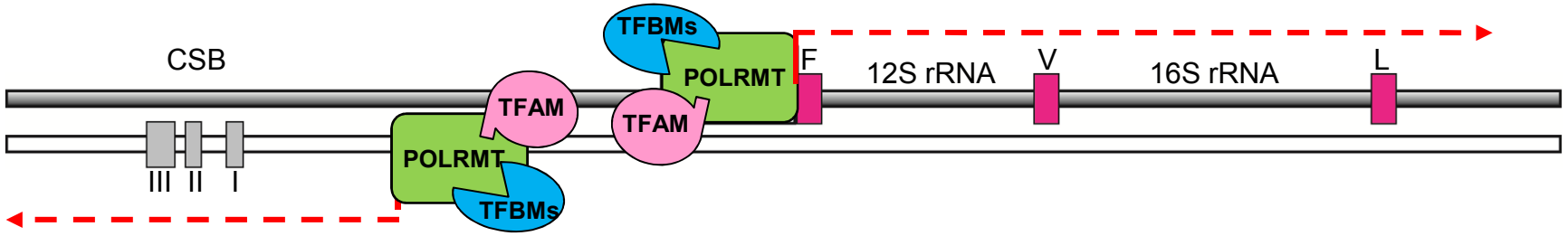
MtDNA expression require nuclear factors



Transcription of mammalian mtDNA



Initiation of mammalian mtDNA transcription



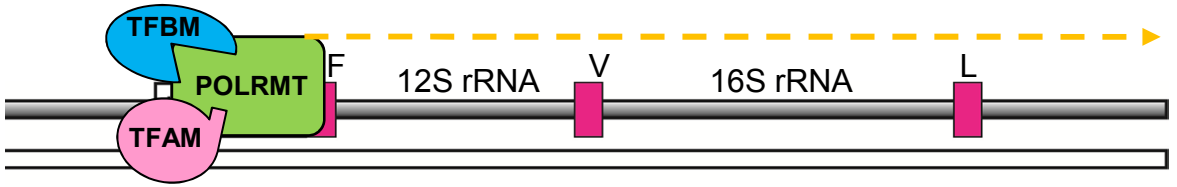
POLRMT : mitochondrial RNA polymerase

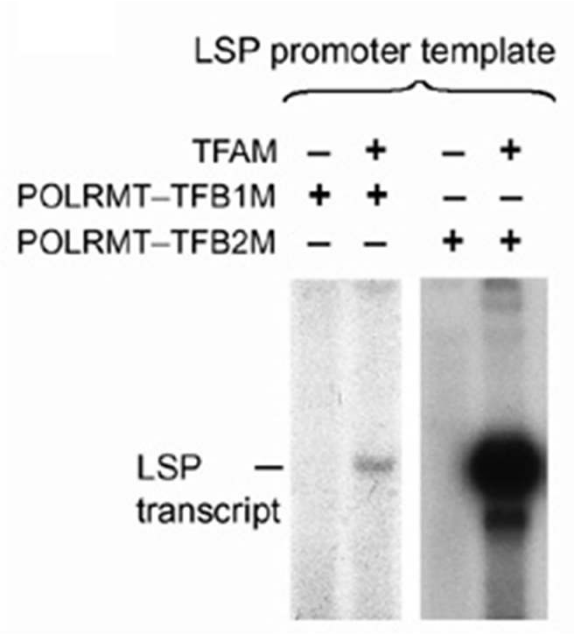
TFAM : mitochondrial transcription factor A

TFB1M-2M : mitochondrial transcription factor B1-2

Falkenberg et al.; Nat Genet (2002)

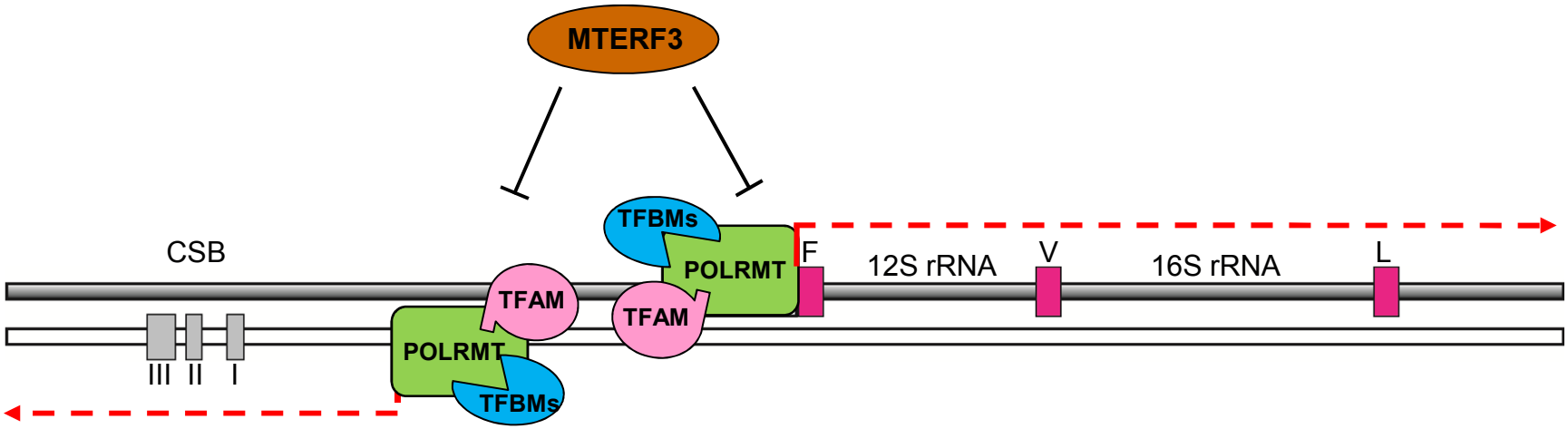
Reconstituted mtDNA transcription system





Falkenberg et al.; Nat Genet (2002)

Repression of mammalian mtDNA transcription



POLRMT : mitochondrial RNA polymerase

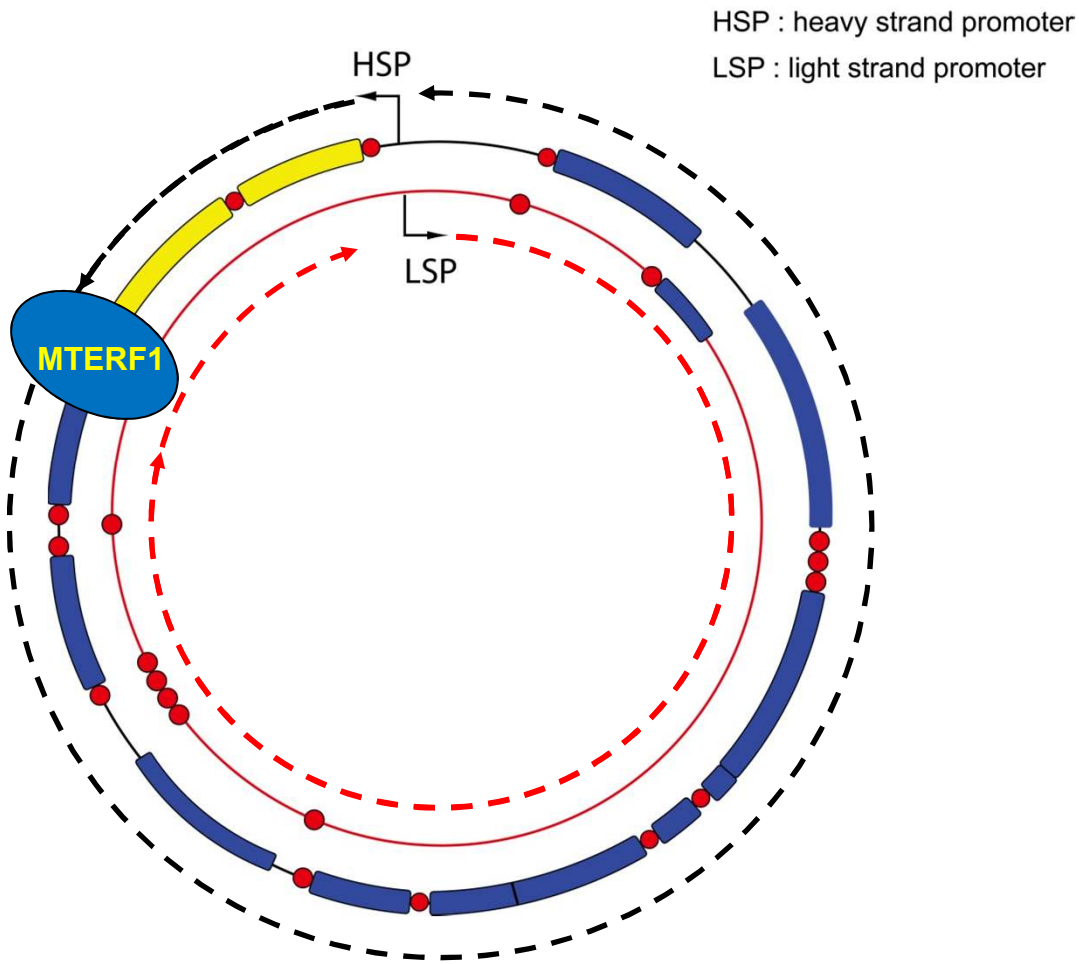
TFAM : mitochondrial transcription factor A

TFB1M-2M : mitochondrial transcription factor B1-2

MTERF3 : mitochondrial transcription termination factor 3

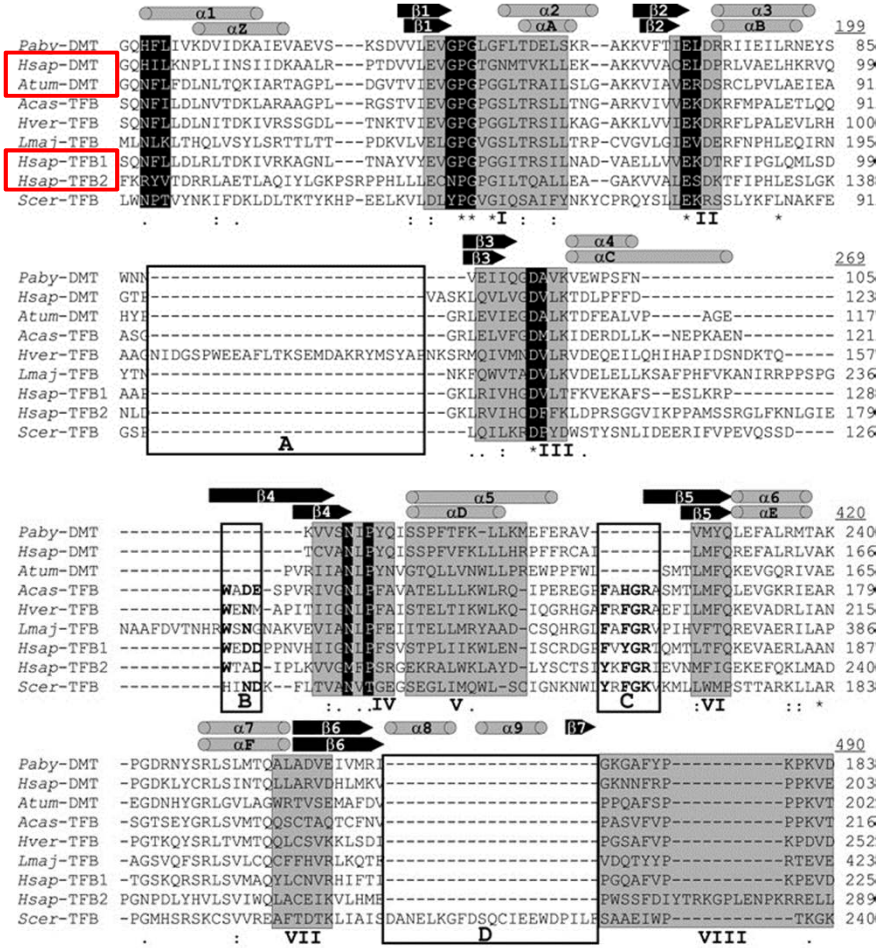
Park et al.; Cell (2007)

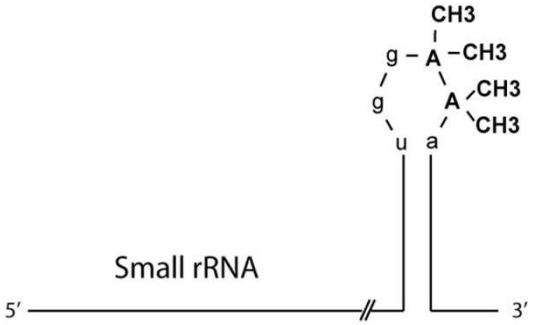
Termination of mammalian mtDNA transcription



In vivo function of TFB1M

TFB1M is homologous to small rRNA methyltransferase

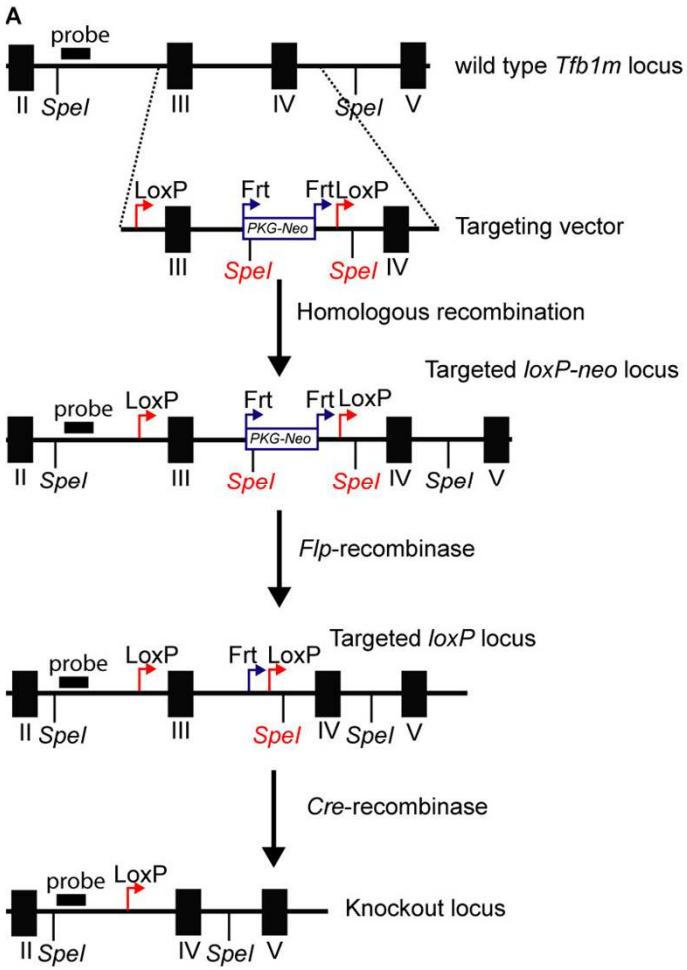


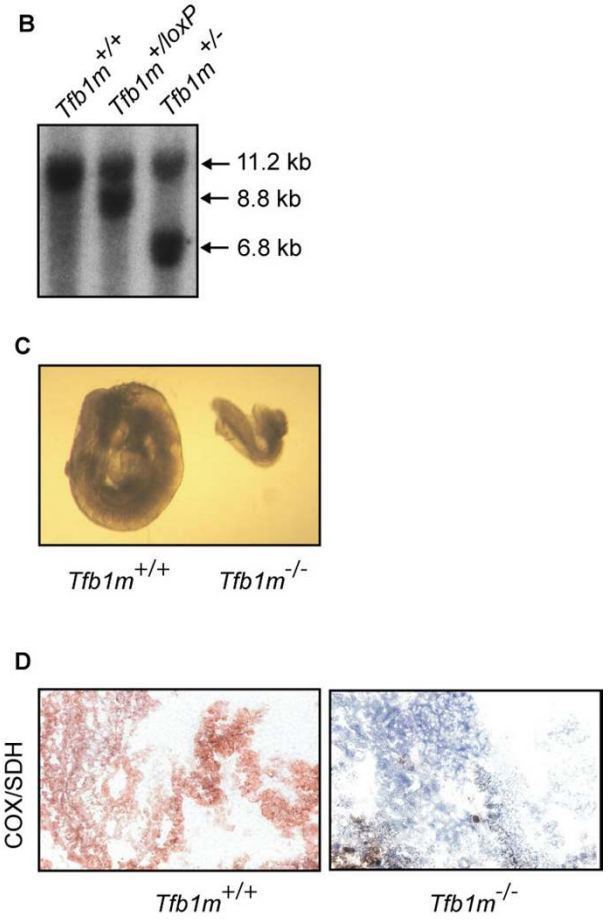


- Dimethylation of small rRNA is conserved

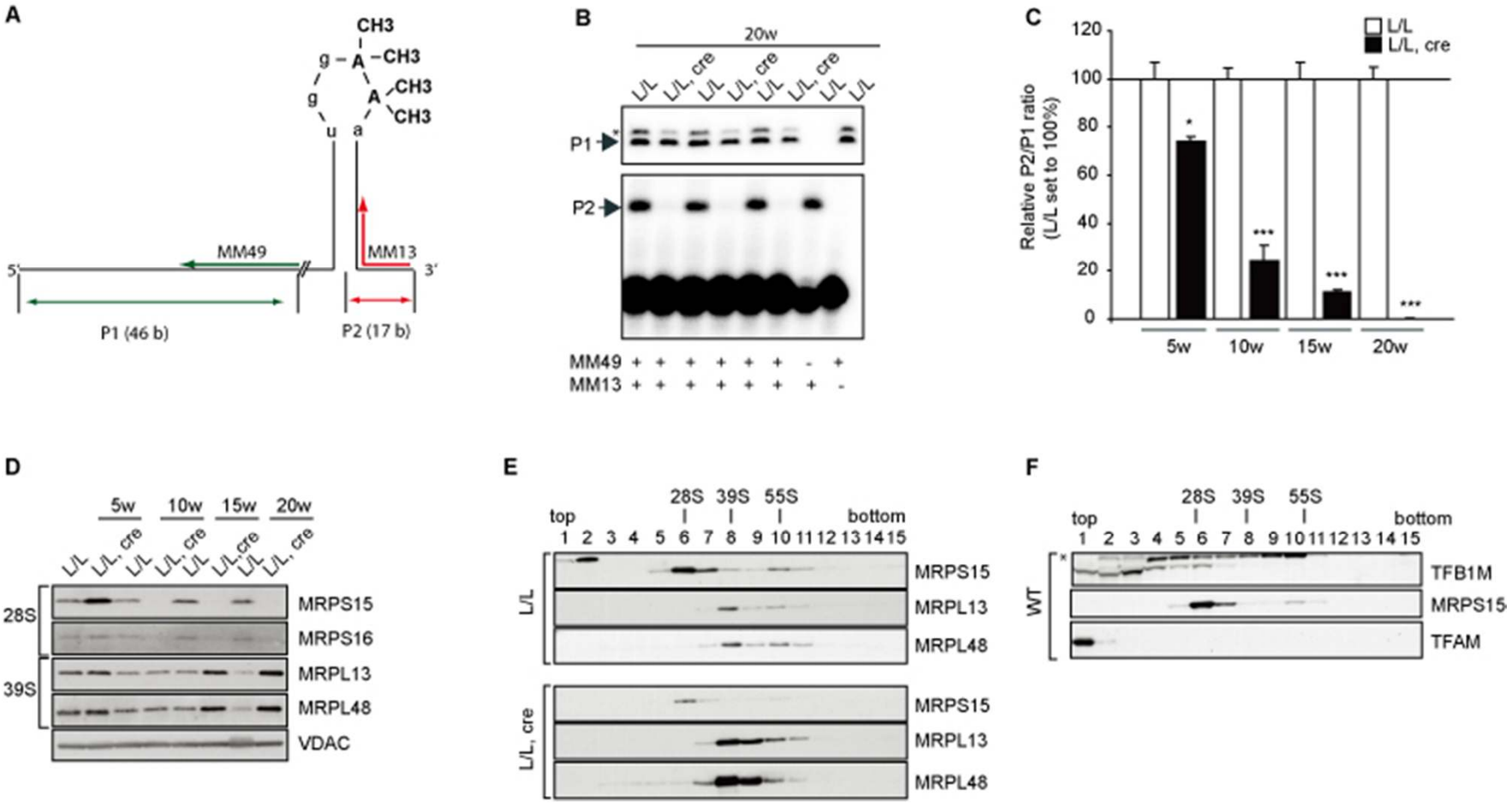
- Important for ribosome assembly

Generation of TFB1M knockout mouse

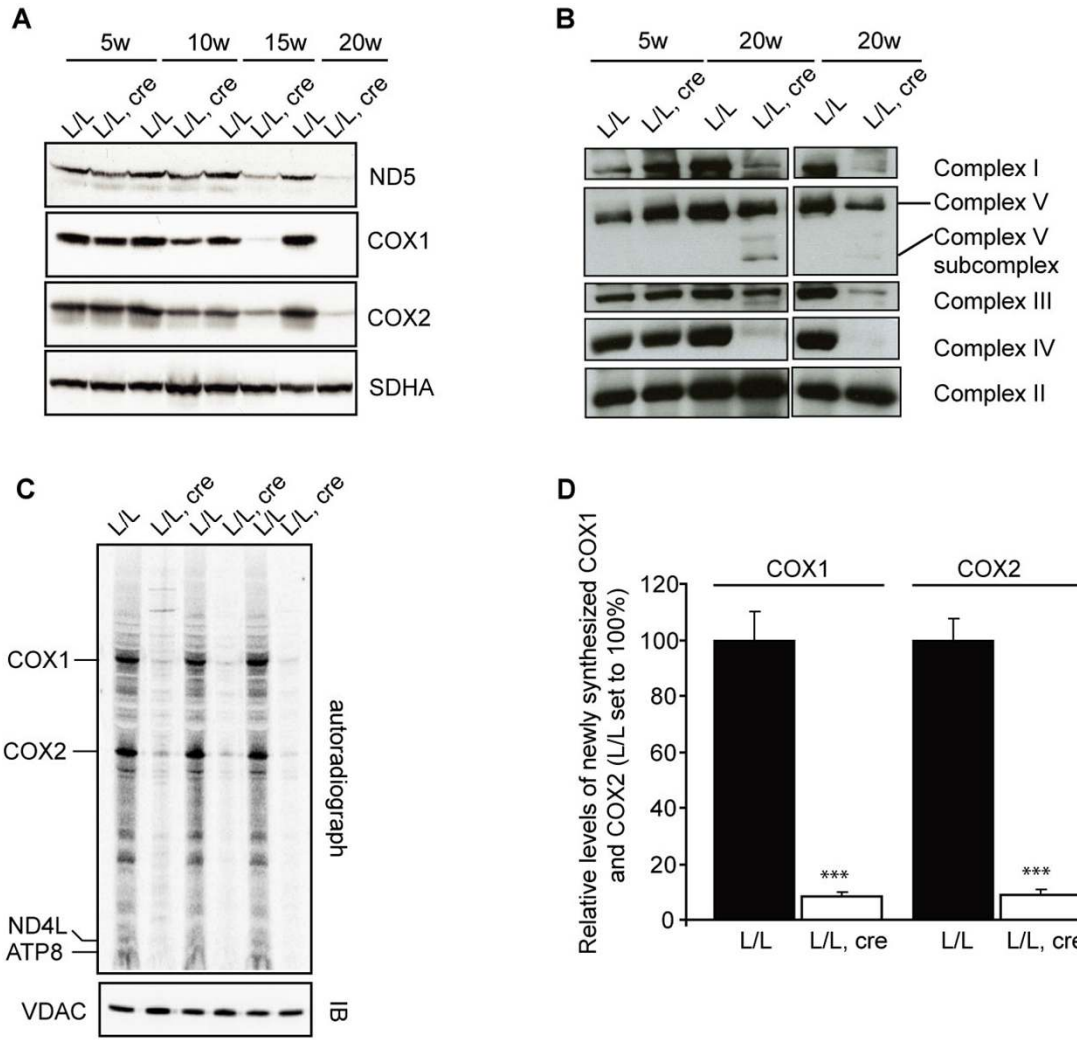




Loss of TFB1M cause lack of 12S rRNA dimethylation



Loss of TFB1M cause defect in mitochondrial translation



TFB1M is mitochondrial 12S rRNA methyltransferase

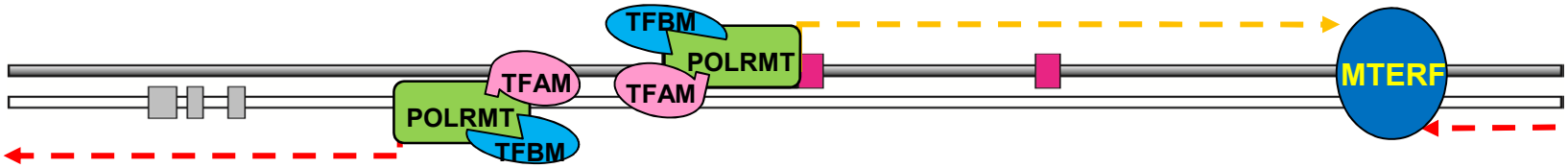
Cell Metabolism
Article

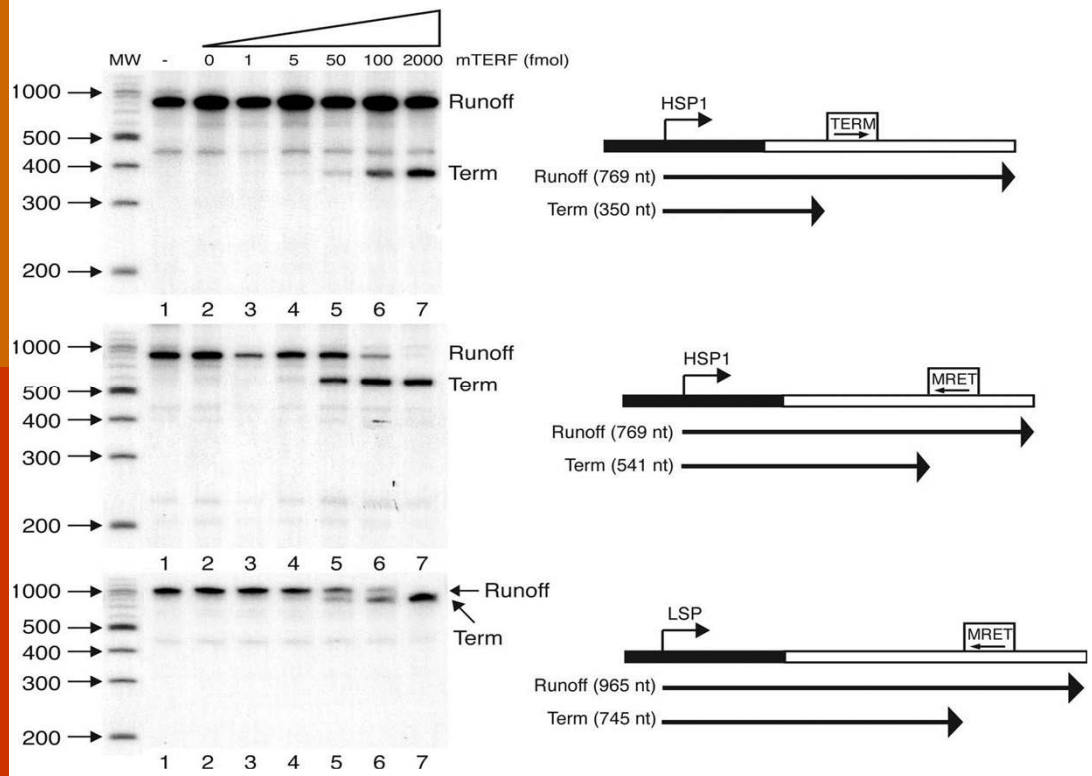
Methylation of 12S rRNA Is Necessary for In Vivo Stability of the Small Subunit of the Mammalian Mitochondrial Ribosome

Metodi D. Metodiev,[1,3] Nicole Lesko,[1] Chan Bae Park,[2] Yolanda Cámara,[1] Yonghong Shi,[1] Rolf Wibom,[1] Kjell Hultenby,[1] Claes M. Gustafsson,[1] and Nils-Göran Larsson[1,3,*]
[1]Department of Laboratory Medicine, Division of Metabolic Diseases, Karolinska Institutet, Stockholm, Sweden
[2]Institute for Medical Sciences, Ajou University School of Medicine, 443-721 Suwon, Korea
[3]Max Planck Institute for Biology of Ageing, Gleueler Strasse 50a, D-50931 Cologne, Germany
*Correspondence: larsson@age.mpg.de
DOI 10.1016/j.cmet.2009.03.001

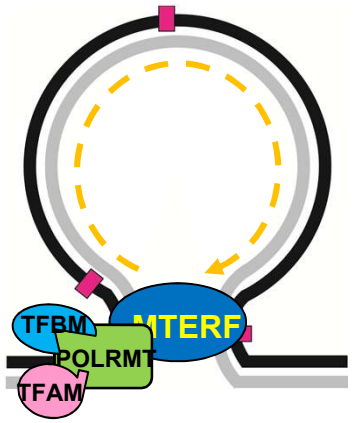
In vivo function of MTERF1

Mitochondrial transcription termination factor1 (MTERF1)



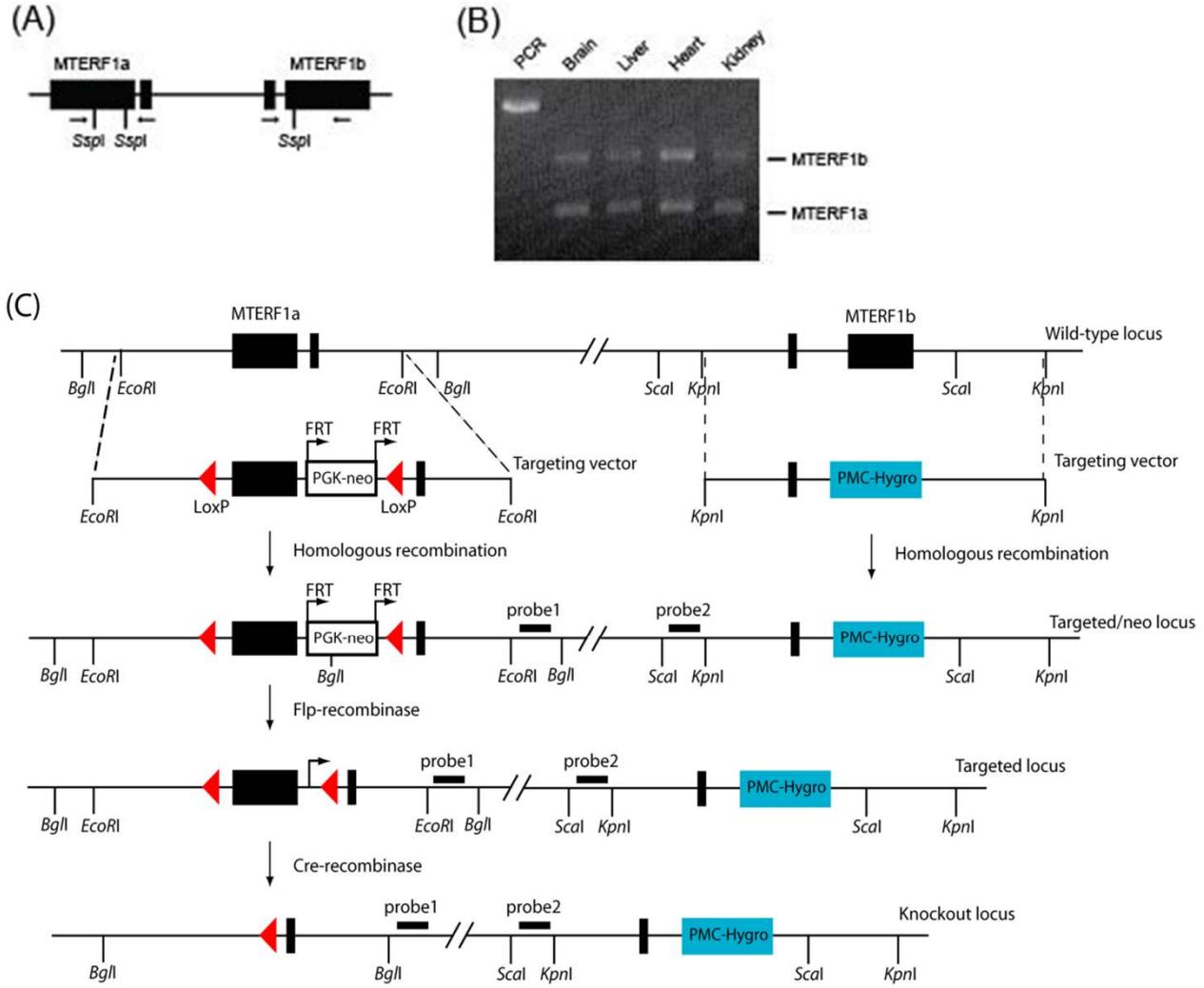


Kruse et al; Cell (1989)
Hess et al; Nature (1991)
Daga et al; JBC (1993)
Fernandez-Silav et al; EMBO J (1995)
Asin-Cayuela et al; JBC (2005)



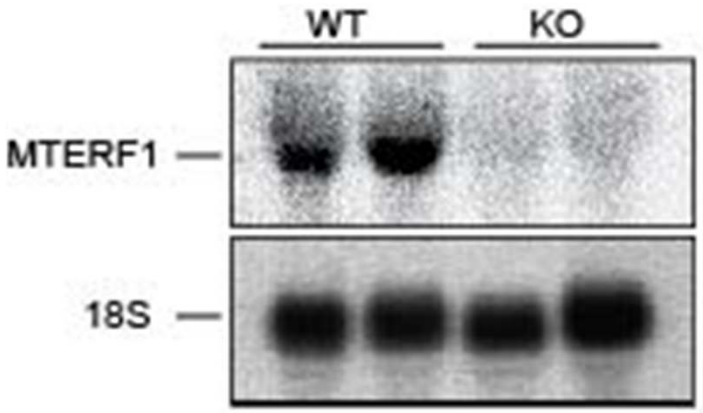
Martin et al;
Cell (2005)

Generation of MTERF1 knockout mouse

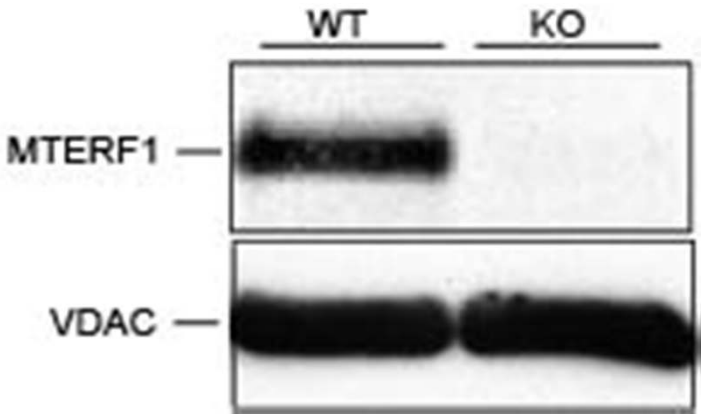


Confirmation of MTERF1 Knockout mouse

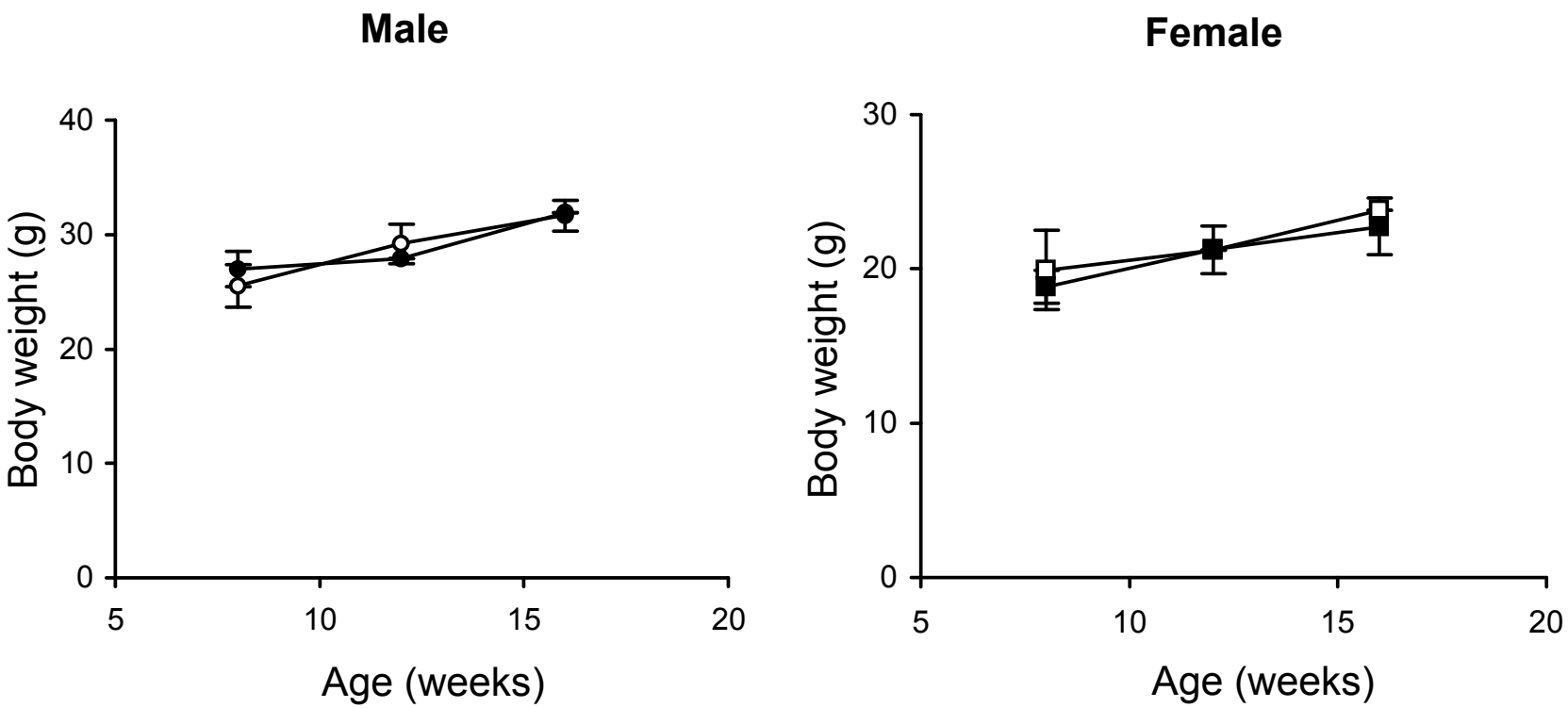
Northern analysis



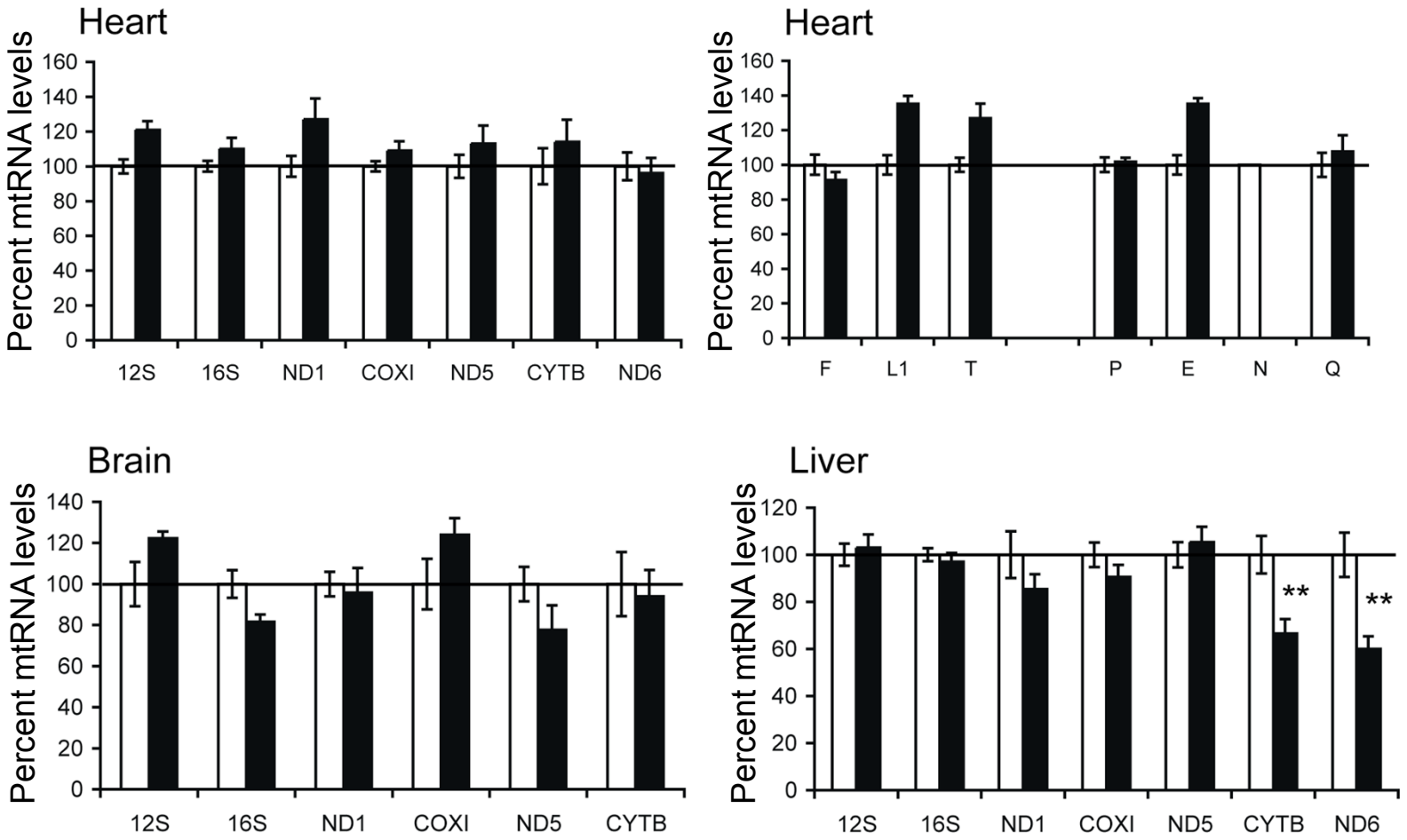
Western analysis



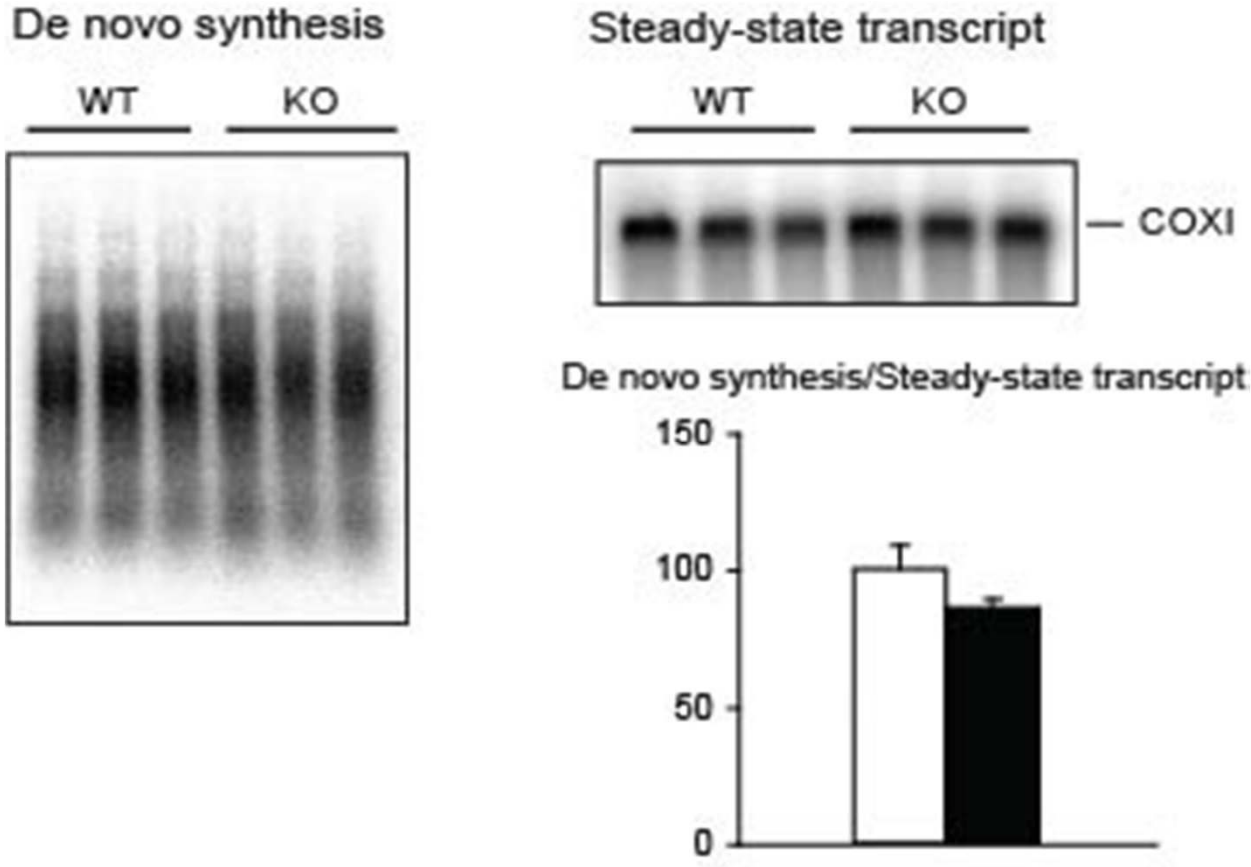
MTERF1 knockout grow normally



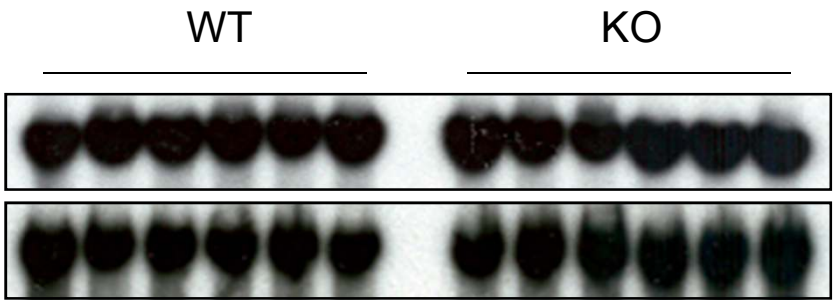
MTERF1 KO mouse have normal level of mtRNAs

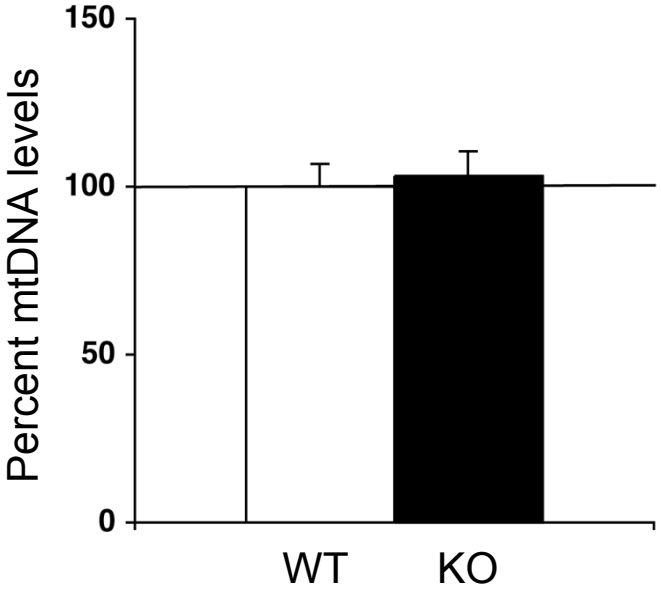


MTERF1 KO mouse have normal *de novo* mtDNA transcription

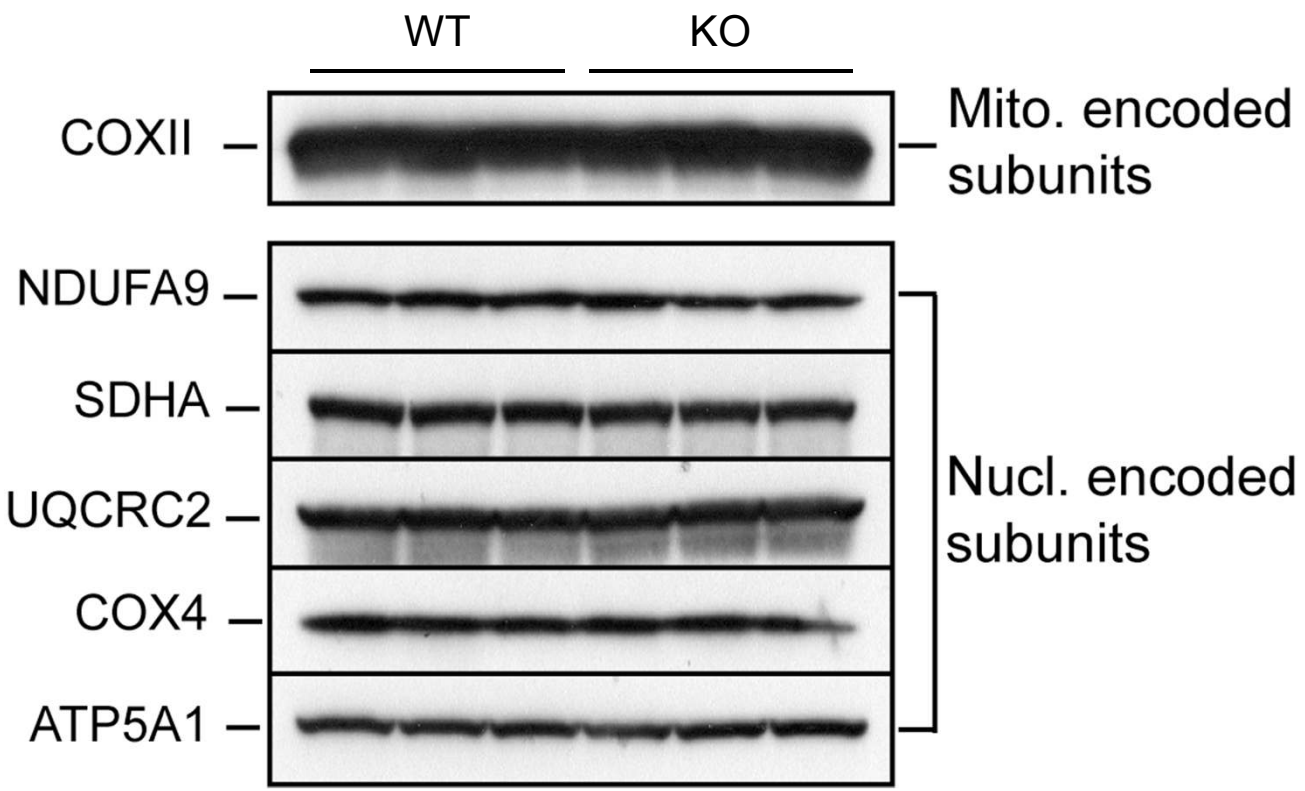


MTERF1 KO mouse have normal level of mtDNA





MTERF1 KO mouse have normal level of RC subunits



Summary

MTERF1 knockout mouse do not show any mtDNA transcription defect

Is MTERF1 mtDNA transcription termination factor?

Novel in vivo MTERF1 function is under investigation

Mitochondrial biogenesis Lab.

Chan Bae Park Group
Ajou Univ. School of Medicine

Bumsoo Kim, Sohyun Kim, Insun Song

Collaborators

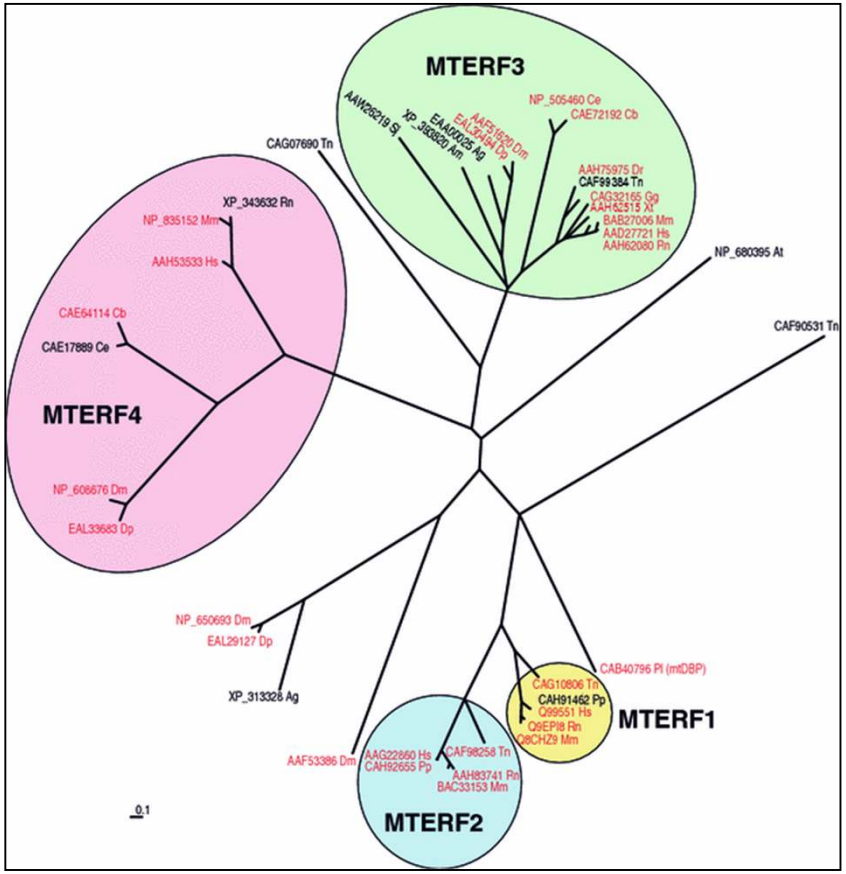
Nils-Goran Larsson Group
Max Planck Institute
Biology for Ageing, Germany

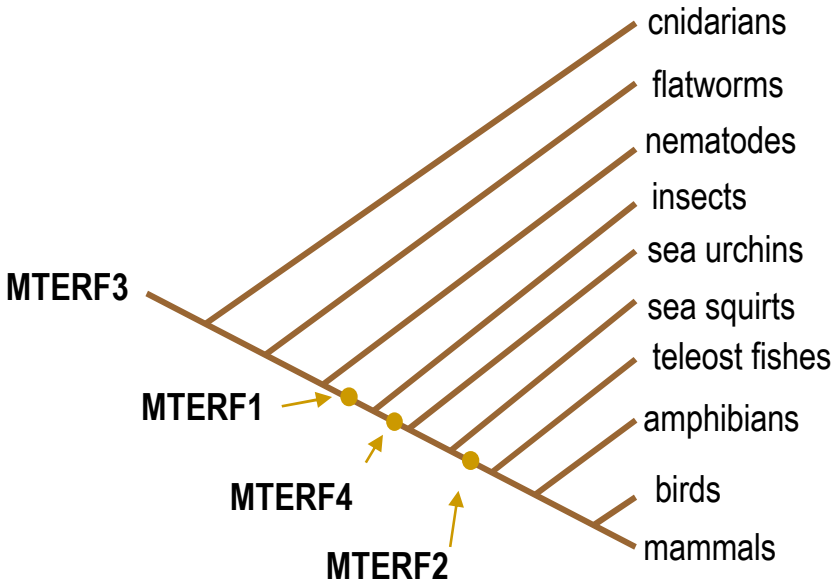
Aleksandar Trifunovic Group
Univ. of Cologne, Germany

Claes Gustafsson Group
Gothenberg Univ., Sweden

Maria Flakenberg Group
Gothenberg Univ., Sweden

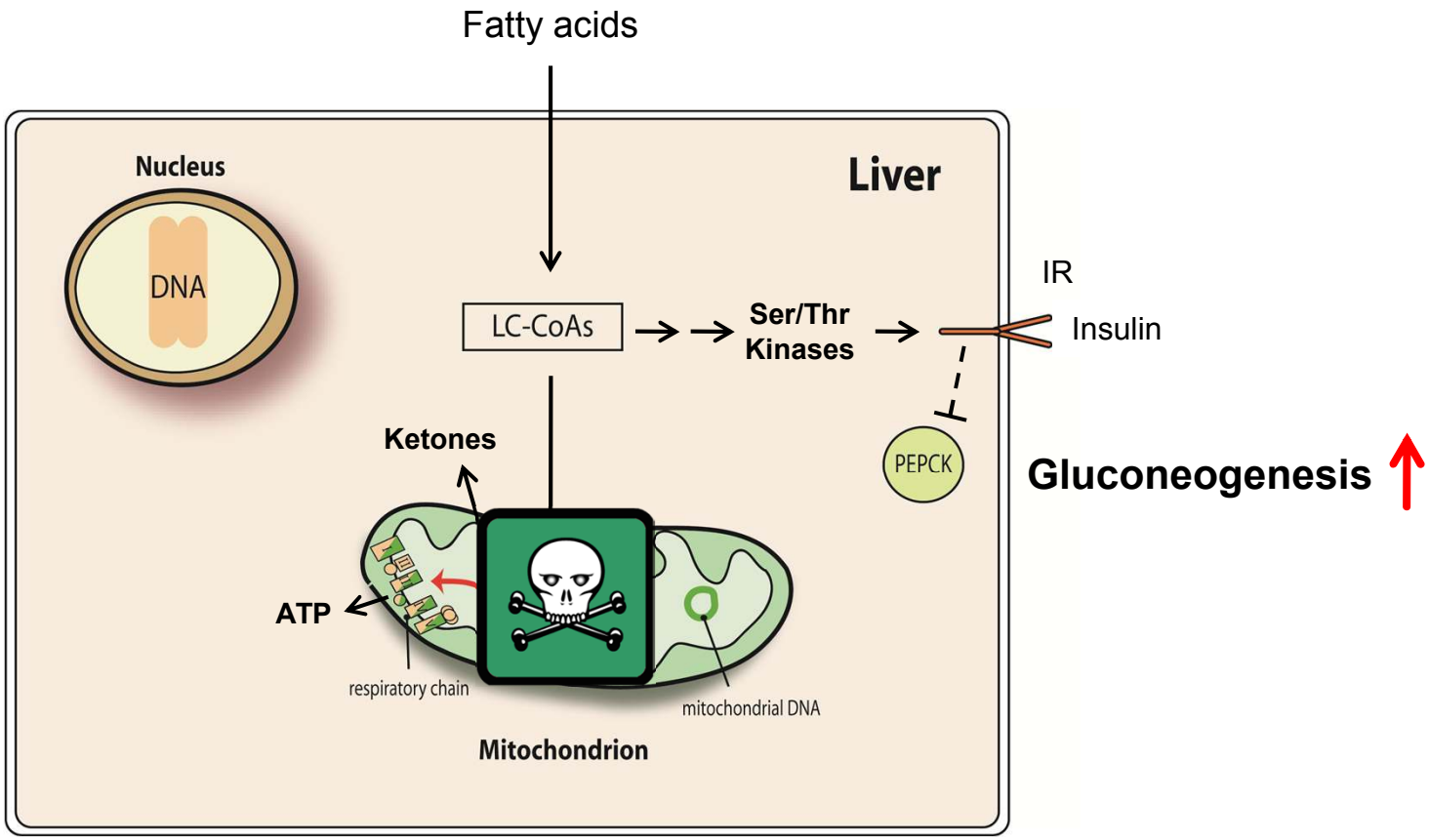
The MTERF family in mammals: MTERF1-4





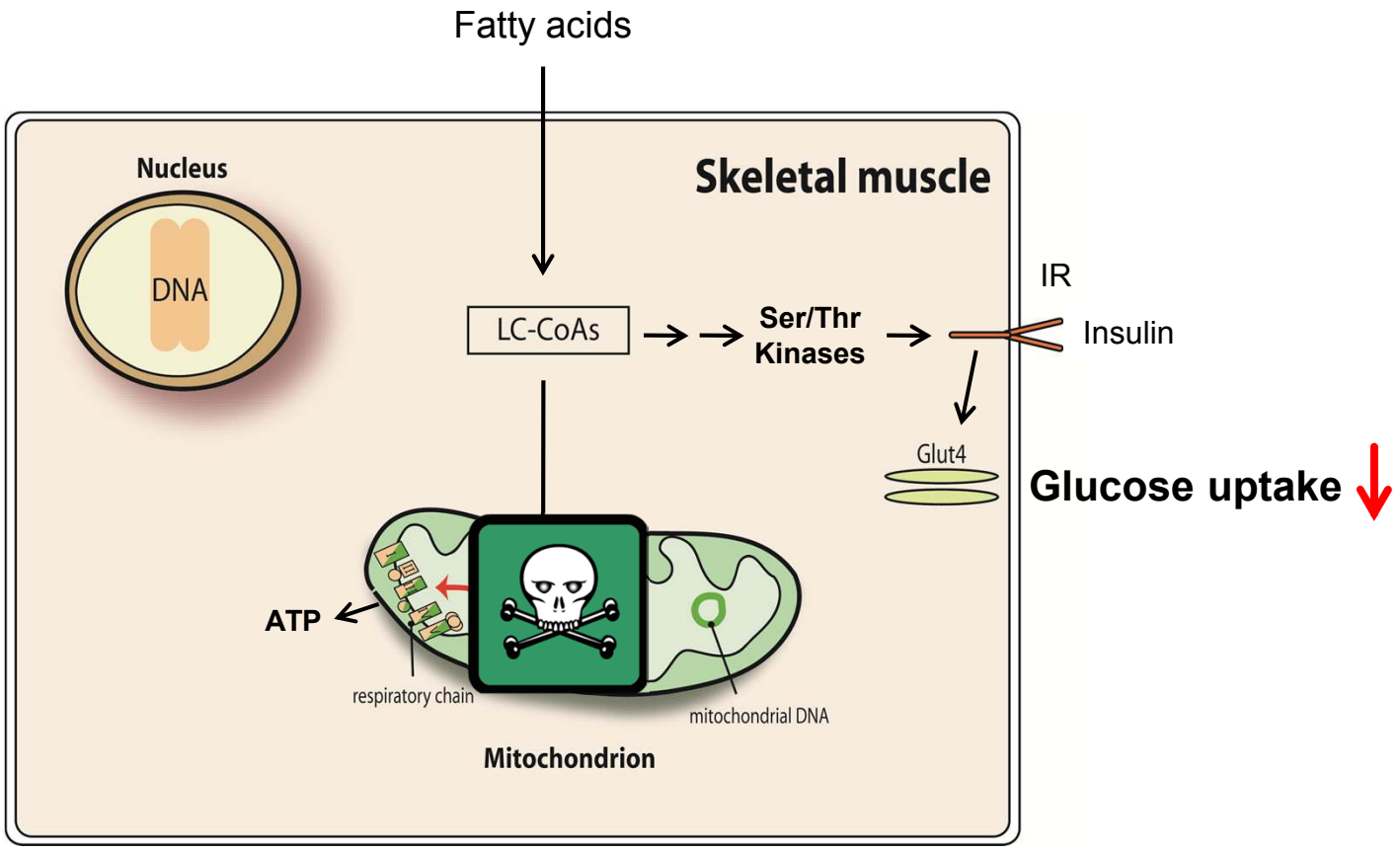
Linder et al; Curr Genet (2005)

Mitochondrial dysfunction in liver and insulin resistance



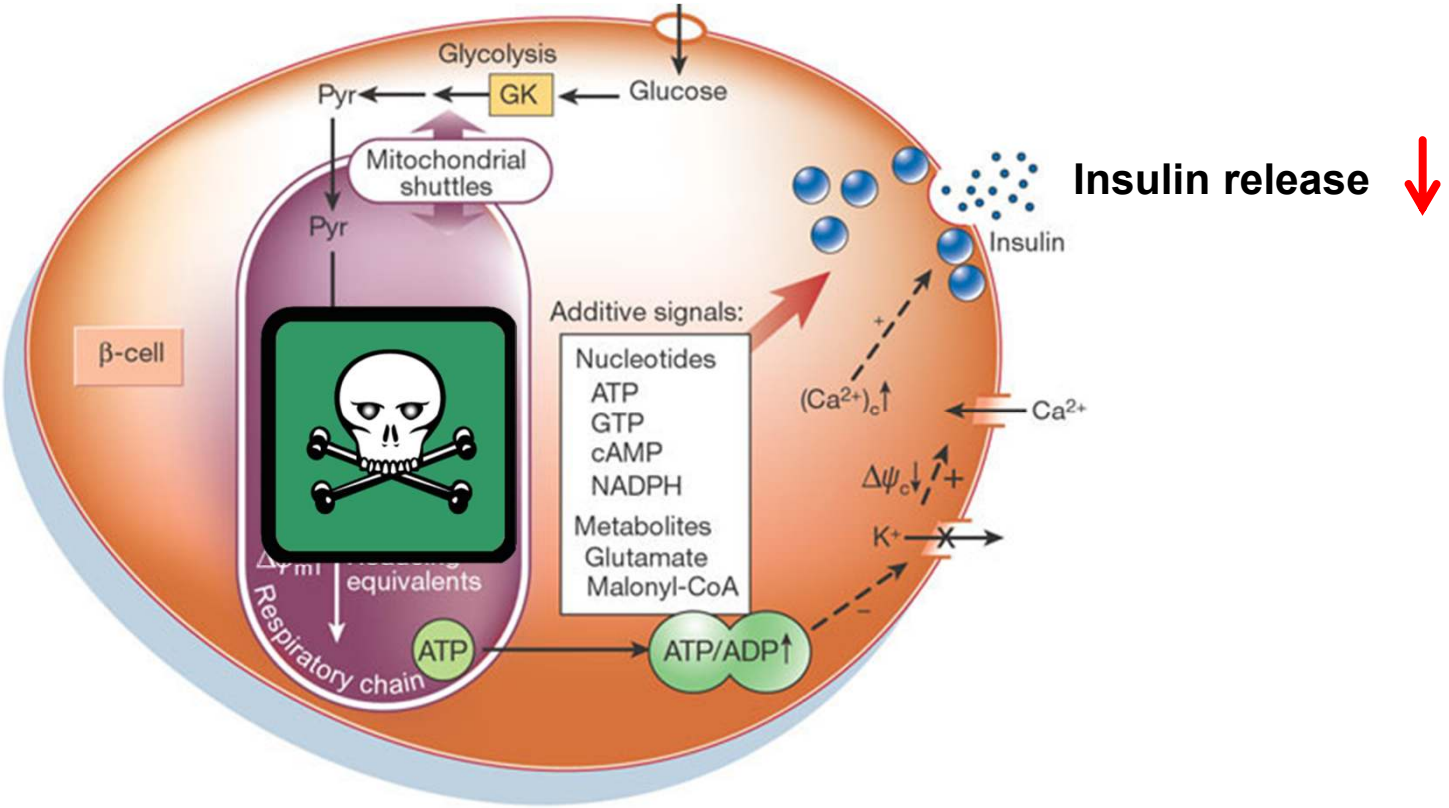
Muoio and Newgard; Nat Rev Mol Cell Biol (2008)

Mitochondrial dysfunction in the muscle and diabetes insulin resistance



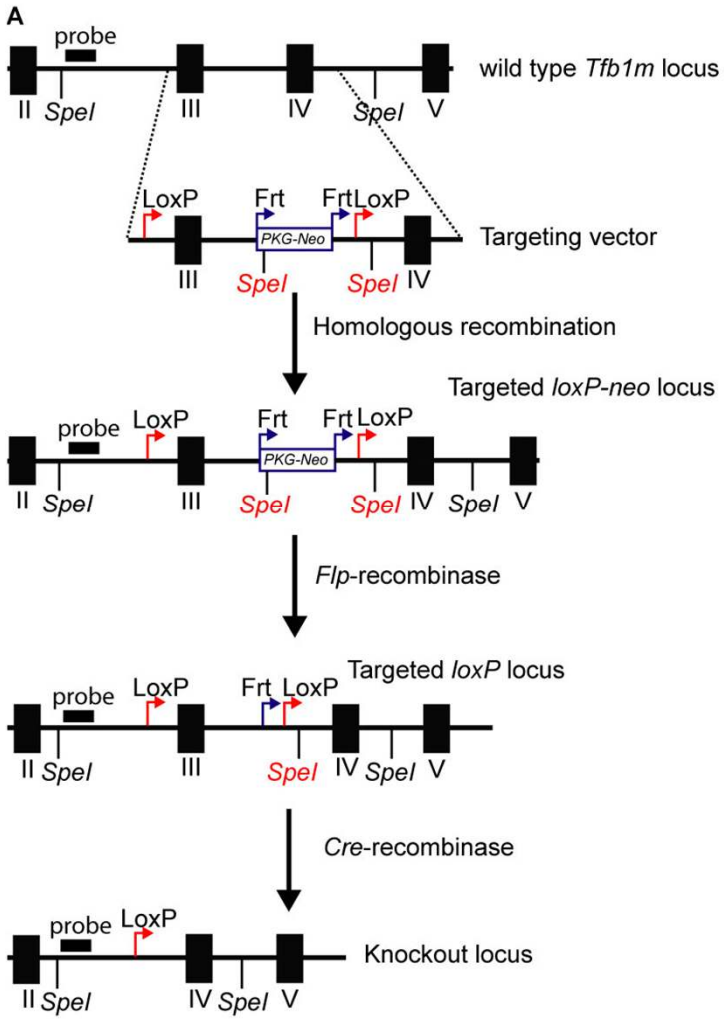
Muoio and Newgard; Nat Rev Mol Cell Biol (2008)

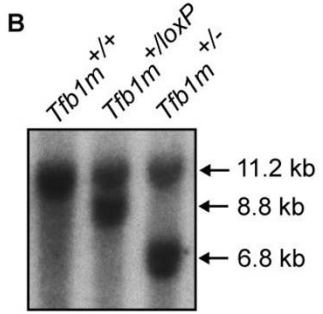
Mitochondrial arecritical in and β-cell function

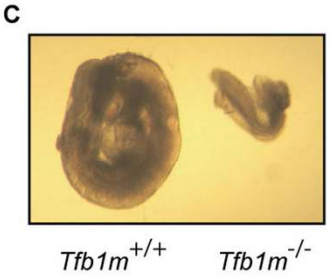


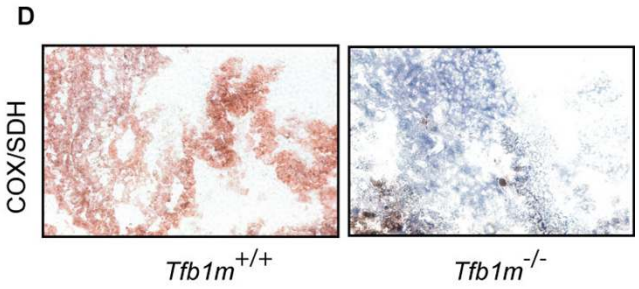
Maechler and Wolleim; Nature(2001)

Generation of TFB1M Knockout Mice









Steady-state levels of mitochondrial transcripts in TFB1M KO herat